EXHIBIT 4.1
DATE 2/12/13
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BIBLIOGRAPHY FOR TANNING BED LEGISLATION

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Report

Tanning bed exposure increases the risk of malignant melanoma

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Abstract

Background Epidemiologic studies have associated tanning bed exposure and cutaneous melanoma. The relationship between the extent of tanning bed exposure and the risk of melanoma has not been elucidated in detail.

Methods Surveys assessing the extent of tanning bed exposure and the history of skin cancer, including malignant melanoma, were collected from academic dermatology clinic patients ($n = 1518$). Of these, 551 (36.3%) completed all components of the survey. The available medical records, including pathology reports ($n = 501$; 33%), were reviewed to confirm cases of skin cancer. Data on potential confounding factors, including indoor vs. outdoor occupation and leisure activities, Fitzpatrick skin type, history of blistering sunburn, use of sunscreen and sun protective clothing, history of phototherapy, and level of education, were assessed and compared.

Results Of the patients surveyed, 487 (32.1%) reported tanning bed exposure. Women aged 45 years or younger accounted for about 60% of all tanning bed users. Seventy-nine cases of malignant melanoma were reported, 22 in women aged 45 years or younger. In the entire cohort, the "ever-use" of tanning beds was found to be a significant risk factor for the development of melanoma [$P < 0.05$; odds ratio (OR), 1.64; 95% confidence interval (95% CI), 1.01–2.67]. The risk was greater in women aged 45 years or younger ($P < 0.05$; OR, 3.22; 95% CI, 1.01–11.46). Patients with a history of melanoma were significantly more likely to report tanning bed sessions exceeding 20 min ($P < 0.01$; OR, 3.18; 95% CI, 1.48–6.82); this association was even stronger for women aged 45 years or younger (OR, 4.12; 95% CI, 1.41–12.02).

Limitations The study was subject to recall bias, included only patients at a midwestern academic practice, and had a relatively low response rate.

Conclusion Exposure to tanning beds increases the risk of malignant melanoma, especially in women aged 45 years or younger. These findings reinforce the hazards of tanning bed exposure.

Introduction

The use of indoor tanning beds remains prevalent despite increasing data on its harmfulness. A recent survey of adolescents found that 28% of females and 7% of males had used tanning booths repeatedly.[1] Evidence is accumulating for the association between tanning bed use and the development of skin cancer.[2–9] Tanning bed users are increasingly aware of these risks, although this knowledge may not deter continued use.[10–12] Many tanning salon patrons erroneously believe that an artificial tan prevents subsequent sunburn and is safer than tanning outdoors.[10,12,13] Tanning bed users report feeling relaxed during indoor tanning,[10] and ultraviolet (UV) tanning for habitual users may be considered a substance-related disorder.[14]

Recent epidemiologic studies have suggested an association between tanning bed/sunlamp exposure and cutaneous melanoma.[5–7,9] Because most reports have focused on the "ever-use" of tanning beds,[2,4–6] the potential relationship between the extent of tanning bed exposure and the risk of melanoma has not been elucidated in detail. Moreover, previous studies have generally considered only a few confounding factors, including sun sensitivity, sun exposure, and socioeconomic status.[3–6] This report further examines the risk of melanoma with tanning bed exposure, and investigates the relationship between the extent of tanning bed exposure and the development of melanoma.

Methods

Institutional review board approval was obtained. We sought to enroll a random sample of patients presenting to our academic dermatology clinic over a 12-month period. Surveys were distributed to 1518 patients, and were fully completed by 551 (36.3%). The demographic parameters collected included self-identified race, age, and education level. The surveys assessed the extent of tanning bed exposure, including "ever-use"

and use in the last 12 months, age at first exposure, season of use, lifetime number of tanning sessions, minutes spent per session, sun protection attitudes and practices, and leisure and occupational sun exposure. The respondent-reported family history of malignant melanoma (MM) was not assessed because of the potential for inaccuracy. The medical records of respondents were then reviewed for a history of actinic keratosis (AK), basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and MM. Crude model risk estimates, chi-squared analyses, and adjusted model risk estimates with binary logistic regression were performed (SPSS for Windows). $P < 0.05$ was the threshold for statistical significance.

Confounding variables

Participants were asked a series of questions related to confounding factors in the development of MM. These factors included age, indoor vs. outdoor occupation and leisure activities, Fitzpatrick skin type, history of blistering sunburn, use of sunscreen and sun protective clothing, history of phototherapy, and level of education. Responses to each question were pooled and then categorized (Table 1) for statistical comparison. The incidence of MM was compared for tanning bed users and nontanning bed users overall, and by isolating each potential confounding variable.

Results

Demographics and UV exposure (Table 1)

Surveys were distributed to 1518 patients in the waiting room of our hospital-based clinic, and all surveys were at least partially completed. All surveys were completed with regard to age, gender, tanning bed use, and self-reported diagnosis of melanoma, as these items were listed first; 551 (36.3%) of the patients completed the entire survey, and these surveys were used to tabulate demographic and medical history data (Table 1). Of the 551 patients fully completing the survey, 337 (61.2%) were females and 214 (38.8%) were males; 498 (90.4%) identified themselves as Caucasian. The ages of the participants were well distributed; 297 of the 551 (53.9%) had completed high school, 121 (22%) had completed college, and 126 (22.9%) had completed graduate or professional school. Of the 551 patients, 359 (65.1%) reported an indoor work environment, 45 (8.2%) reported an outdoor work environment, and 132 (24%) reported working both indoors and outdoors; 348 of the 551 participants (63.2%) recalled experiencing sunburn in the past, whereas 203 (36.8%) did not. Of those who had experienced sunburn, over half (196/348, 56.3%) recalled two to five sunburn episodes, 72 (20.7%) reported a single episode, 31 (8.9%) reported six to ten episodes, and 17 (4.9%) reported more than eleven episodes. Of all 551 respondents, 101 (18.3%) reported daily application of sunscreen, 108 (19.6%) reported never using sunscreen, and 335 (60.8%) used sunscreen occasionally.

Table 1 Demographic and ultraviolet (UV) exposure characteristics of the study population

Characteristic	Number (%)
Gender	
Female	337 (61.2)
Male	214 (38.8)
Age (years)	
< 18	48 (8.7)
18–29	103 (18.7)
30–39	84 (15.2)
40–49	91 (16.5)
50–59	84 (15.2)
> 60	141 (25.6)
Race	
Caucasian	498
Asian	7
Hispanic	7
African-American	6
Other/unspecified	33
Tendency to tan	
Easily	162 (29.4)
Moderately	222 (40.3)
Burn rather than tan	80 (14.5)
Unspecified	87 (15.8)
Education	
High school	297 (53.9)
College	121 (22)
Graduate/professional	126 (22.9)
Unspecified	7 (1.3)
Work Environment	
Indoor	359 (65.2)
Outdoor	45 (8.2)
Both	132 (24.0)
Unspecified	15 (2.7)
Sunburn in past	
No	203 (36.8)
Yes	348 (63.2)
Number of sunburn episodes	
1	72 (20.7)
2–5	196 (56.3)
6–10	31 (8.9)
11+	17 (4.9)
Previous history of	
AK	65 (13)
BCC	73 (14.6)
SCC	27 (5.4)
MM	29 (5.8)

Demographic and UV exposure parameters are shown for 551 patients completing the entire survey. The history of AK and malignancy is shown for 501 of these patients for whom medical records and pathology reports were available. AK, actinic keratosis; BCC, basal cell carcinoma; MM, malignant melanoma; SCC, squamous cell carcinoma.

Incidence of skin cancer and skin premalignancy

Of the 551 patients fully completing the questionnaire, medical records were available for 501 (90.9%). Of these, 65

Table 2 Relationship between reported tanning bed exposure and malignant melanoma

	History of malignant melanoma (%)	No history of malignant melanoma (%)	Odds ratio (95% CI)
Ever used tanning bed (all respondents; $n = 487$)	34 (7)*	453 (93)	1.65 (1.01–2.67)
Never used tanning bed (all respondents; $n = 1031$)	45 (4.4)	986 (95.6)	
Ever used tanning bed (female respondents age ≤ 45 years; $n = 279$)	18 (6.5)*	261 (93.5)	3.22 (1.01–11.46)
Never used tanning bed (female respondents age ≤ 45 years; $n = 191$)	4 (2.1)	187 (97.9)	

CI, confidence interval.
*$P < 0.05$ vs. nontanning bed users.

Table 3 Amount of tanning bed use in patients with and without melanoma

	Used tanning beds ≥ 20 sessions (%)	Odds ratio (95% CI)	Used tanning beds ≥ 20 min per session (%)	Odds ratio (95% CI)
Ever used tanning beds ($n = 487$)				
History of melanoma ($n = 34$)	21 (62)	1.82 (0.85–3.95)	16 (48)*	3.18 (1.48–6.82)*
No history of melanoma ($n = 453$)	213 (47)		99 (22)	
Women aged ≤ 45 years ($n = 279$)				
History of melanoma ($n = 18$)	14 (78)	3.27 (0.97–12.1)	9 (50)*	4.12 (1.41–12.02)*
No history of melanoma ($n = 261$)	135 (52)		51 (19.5)	

CI, confidence interval.
*$P < 0.01$ vs. no history of melanoma.

(13%) had been diagnosed with AKs (mean age, 63.7 ± 11.1 years), 73 (14.6%) with BCC (mean age, 61.6 ± 12.1 years), 27 (5.4%) with SCC (mean age, 64.6 ± 9.7 years), and 29 (5.8%) with MM (mean age, 49.3 ± 15.3 years) (see Table 1).

Tanning bed users

Of the 1518 patients surveyed, 487 (32.1%) reported a history of tanning bed exposure. Women aged 45 years or younger accounted for 60% (292/487) of all tanning bed users, with 59.3% (279/470) of these women reporting a history of tanning bed use compared with 24.4% (108/442) of women aged over 45 years. Subgroup analysis isolating each of the demographic factors and potentially confounding variables did not otherwise predict the utilization of tanning beds.

Incidence of MM

Of the 1518 respondents, 79 (5.2%) reported a previous history of MM. MM was verified via a pathology report in the medical records of 29 of the 501 patients (5.8%) for whom these were available. Of the individuals who had used a tanning bed at least once, 7.0% (34/487) reported a history of MM; in persons who denied the use of tanning beds, 4.4% (45/1031) reported a history of MM ($P < 0.05$; Table 2). Amongst the entire cohort, the "ever-use" of a tanning bed was a statistically significant risk factor for the development of melanoma [$P < 0.05$; odds ratio (OR), 1.64; 95% confidence interval (95% CI), 1.01–2.67] (Table 2). In women aged 45 years or younger, the "ever-use" of a tanning bed was an even greater risk factor for the development of melanoma after controlling for the same variables; 18 of 279 women under the age of 45 years who had used a tanning bed reported a previous diagnosis of melanoma, whereas four of 191 women under the age of 45 years who denied ever using a tanning bed reported a previous diagnosis of melanoma ($P < 0.05$; OR, 3.19; Table 2). Subgroup analysis isolating each of the potentially confounding variables did not reveal any other significant associations with melanoma.

Duration and number of tanning sessions (Table 3)

Admitted tanning bed users with a history of melanoma were more likely to report greater than 20 tanning bed exposures than were tanning bed users without melanoma [21/34 (61.8%) vs. 213/453 (47.2%)], although this was not statistically significant. Admitted tanning bed users with melanoma reported a significantly greater average time spent per tanning bed session, with 16 of 34 (48%) reporting sessions greater than 20 min, compared with 99 of 453 (22%) tanning bed users with no history of melanoma ($P < 0.01$; OR, 3.18; 95%

CI, 1.48–6.82). Female tanning bed users aged 45 years and younger with a history of MM ($n = 18$) spent more time per session [9/18 (50%) with sessions averaging over 20 min; $P < 0.01$] than those with no history of melanoma [51/261 (20%) with sessions averaging over 20 min; $P < 0.01$; OR, 4.12; 95% CI, 1.41–12.02] (Table 3).

A greater percentage of women aged 45 years and younger with a history of melanoma reported 20 or more lifetime sessions (14/18 or 78%) than did women aged over 45 years without a history of melanoma (135/261 or 52%), although this was not statistically significant.

Discussion

In this study, 32% of survey respondents had used a tanning bed at least once, a figure comparable with past studies on tanning bed behavior.[7,14,15] Consistent with other studies, tanning bed users were frequently young women.[10,14,16–19] We also found evidence of an increasing risk of melanoma with increasing use of tanning beds, as measured by both the number and duration of tanning sessions. In our binary logistic regression analyses of the "ever-use" of a tanning bed and the variables listed above, tanning bed exposure was a significant risk factor for melanoma in all respondents and, in particular, for women aged 45 years and younger. This concurs with several previous studies that have reported a positive association between sunlamp/sunbed use and melanoma.[3–6,20,21]

A recent meta-analysis of nine case–control studies and one cohort study found a positive association (OR, 1.25) of having ever been exposed to a tanning bed and the risk of melanoma.[9] Swerdlow and Weinstock[22] reviewed 19 case–control studies examining melanoma and tanning bed exposure. Fewer than half of these studies accounted for confounding factors, and most did not consider the frequency or duration of tanning bed exposure.[22] Previous studies in the literature have considered only a few possible confounding factors.[3–6,23] Chen *et al.*[7] found that those who first used sunlamps before the age of 25 years had a higher risk for melanoma than those who first used sunlamps later in life. Similarly, Westerdahl *et al.*[20] found that, for those younger than 36 years of age who regularly used an indoor tanning lamp, the risk of melanoma was 8.1 times greater than for "never-users."

The molecular basis of UV photocarcinogenesis is well known. Most modern tanning units produce mainly UV-A and less than 5% UV-B,[13,24,25] although this amount of UV-B irradiation exceeds that in natural sunlight, and is sufficient to suppress cutaneous immunity.[26] Bech-Thomsen *et al.*[27] reported a linear relationship between tumor development and the content of UV-B in UV tanning sources. Recently, UV-B has been shown to initiate melanoma in an animal model.[28] UV-A radiation penetrates the skin deeply,[8,20] causes photoaugmentation and immunosuppression, and induces DNA damage via the production of reactive oxygen molecules.[8,29,30] Therefore, it probably plays a contributory role in carcinogenesis.[8]

Our study has several limitations. Only 36% of the participants completed the survey entirely. The survey was relatively lengthy, was administered in our clinic waiting room, and was collected at the conclusion of the clinic visit. The degree of survey completion related directly to the waiting time, such that the response rate is not surprising. Tanning bed users often sunbathe, making it difficult to separate the effects of artificial and natural UV irradiation. We were unable to control for the use of photosensitizing medications, and survey responses were subject to recall bias. Although we were concerned that the surveyed patients might confuse the diagnosis of MM with other forms of skin cancer, comparison of the survey responses with available pathologic reports (representing about one-third of the respondents) showed good agreement, with a 5–6% incidence of melanoma in both cases. The retrospective nature of the study made it impractical to investigate the lapse of time between tanning bed use and the diagnosis of MM, and whether the diagnosis of melanoma deterred further use of tanning beds in individual patients. Moreover, our results were derived solely from a midwestern academic setting; it is possible that surveys from different climate and practice settings could yield different results.

In conclusion, these results suggest that tanning bed exposure is a significant risk factor for MM, especially in women aged 45 years and younger. This study also correlates the extent of tanning bed exposure and the risk of the development of cutaneous melanoma. These findings reinforce public health urgency to increase the awareness of the potential health hazard of tanning bed exposure.

Acknowledgment

Supported by a Skin Cancer Foundation Photobiology grant.

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Published OnlineFirst on May 26, 2010 as 10.1158/1055-9965.EPI-09-1

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Indoor Tanning and Risk of Melanoma: A Case-Control Study in a Highly Exposed Population

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Abstract

Background: Indoor tanning has been only weakly associated with melanoma risk; most reports were unable to adjust for sun exposure, confirm a dose-response, or examine specific tanning devices. A population-based case-control study was conducted to address these limitations.

Methods: Cases of invasive cutaneous melanoma, diagnosed in Minnesota between 2004 and 2007 at ages 25 to 59, were ascertained from a statewide cancer registry; age-matched and gender-matched controls were randomly selected from state driver's license lists. Self-administered questionnaires and telephone interviews included information on ever use of indoor tanning, types of device used, initiation age, period of use, dose, duration, and indoor tanning–related burns. Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for known melanoma risk factors.

Results: Among 1,167 cases and 1,101 controls, 62.9% of cases and 51.1% of controls had tanned indoors (adjusted OR 1.74; 95% CI, 1.42-2.14). Melanoma risk was pronounced among users of UVB-enhanced (adjusted OR, 2.86; 95% CI, 2.03-4.03) and primarily UVA-emitting devices (adjusted OR, 4.44; 95% CI, 2.45-8.02). Risk increased with use: years ($P < 0.006$), hours ($P < 0.0001$), or sessions ($P = 0.0002$). ORs were elevated within each initiation age category; among indoor tanners, years used was more relevant for melanoma development.

Conclusions: In a highly exposed population, frequent indoor tanning increased melanoma risk, regardless of age when indoor tanning began. Elevated risks were observed across devices.

Impact: This study overcomes some of the limitations of earlier reports and provides strong support for the recent declaration by the IARC that tanning devices are carcinogenic in humans. *Cancer Epidemiol Biomarkers Prev; 19(6); 1557–68. ©2010 AACR.*

Introduction

Between 1997 and 2006, melanoma incidence increased 2.2% and 2.1% annually in the United States among Caucasian males and females, respectively (1). These trends have resulted in melanoma ranking first among men and second among women as the fastest increasing cancer for the 10 most common cancers in Caucasians, even as most common cancers are declining or stable. Intense, intermittent solar UV radiation has long been thought to account for the rise in melanoma (2). Indoor tanning is an artificial source of intermittent UV radiation exposure that has gained in popularity since the early 1980s. The indoor tanning industry estimates that approximately 30 million Americans visit indoor tanning salons each year (3). A recent report based on data from 116 cities in the United States found that the average number of tanning salons exceeded the average number of Starbucks or McDonald's (4).

In 2009, the IARC classified tanning devices as carcinogenic to humans (5). The IARC report may have little effect on indoor tanning use in the United States, in part, because the industry has used limitations of the studies reviewed by the IARC and hypotheses regarding potential health benefits, such as vitamin D, to counter possible health concerns (6). With at least 29 reports to date (7-35), past history of indoor tanning has been only weakly associated with melanoma (ref. 5; the IARC reported a summary odds ratio of 1.15; 95% CI, 1.00-1.31 based on 19 studies), and limitations of these studies include the lack of information on sun exposure (a known correlate of indoor tanning use; ref. 36) in the majority of studies, and a low or presumed low prevalence of exposure to indoor tanning. Only 11 studies have provided some detail about the exposure, but none measured dose-response or

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doi: 10.1158/1055-9965.EPI-09-1249

reported on age of initiation in the same manner (11, 17, 21-23, 25, 27, 28, 30-32). Consequently, the evidence that melanoma occurrence increases with frequent indoor tanning use is limited. In addition, only three studies have examined melanomas in relation to indoor tanning use during adolescence (30-32), when indoor tanning is most likely to be initiated (37). Although moderately strong associations have been reported, point estimates were imprecise, perhaps due to the low frequency of exposure (30, 32) or number of events (31).

Information on the risk of melanoma associated with specific devices is also lacking. Tanning devices emit both UVB and UVA. The UVB component has been considered to be the putative factor for skin carcinogenesis, but cutaneous melanocytes absorb both UVB and UVA (38), and mechanisms have been proposed by which UVA might lead to skin cancer, including indirect damage to DNA via reactive oxygen species (39-41). A complicating factor is that devices have changed over time. For example, devices available prior to the 1980s emitted much higher levels of UVB compared with normal solar UV radiation. These were followed by the introduction in the 1980s of devices emitting primarily UVA to address the public's concern about burning (42-45). In the 1990s, UVB was reintroduced in high-speed or high-intensity devices to produce deeper tans, and high-pressure devices emitting almost exclusively UVA also became available. Year of use or device type could serve as proxies for UVB versus UVA exposure in epidemiologic studies. However, in most studies, cases were diagnosed prior to 1990, and only a few studies have measured device- or period-specific exposure (21, 23, 27, 30-32). Although the IARC report designated UVA as "carcinogenic" in humans, device- and period-specific results from epidemiologic studies have been inconclusive with respect to melanoma.

In 2004, we initiated the Skin Health Study, a population-based case-control study of indoor tanning in relation to risk of melanoma, that was specifically designed to address the limitations of prior research. The study was conducted in Minnesota, a state with documented high prevalence of the behavior (37). We collected more detailed information than most studies to assess not only melanoma risk associated with frequent use, years of use, and age at which use began, but also with specific devices and period of use to distinguish exposure to UVB or UVA. We also obtained information on known confounders and enrolled a sufficiently large sample size to allow for subgroup analyses which have rarely been possible. Our results are presented here.

Materials and Methods

Ascertainment and recruitment of cases and controls

The Skin Health Study was approved by the Institutional Review Board at the University of Minnesota. Cases were ascertained by the Minnesota Cancer Surveillance System, a population-based, statewide cancer registry. Individuals with invasive cutaneous melanoma, any histologic type, diagnosed between July 2004 and December 2007, between the ages of 25 and 59, with a state driver's license or state identification card, were eligible to participate. The lower age limit allowed for a latency period for melanoma development among indoor tanning users exposed during adolescence; age was truncated at 59 years because indoor tanning decreases with age. In accordance with state laws, the cancer registry first obtained physician permission for research staff to contact his or her patient before releasing case information to research staff; consent was assumed after allowing sufficient time for physician response. Controls were randomly selected from the Minnesota state driver's license list (which includes persons with state identification cards) and frequency-matched to cases in a 1:1 ratio on age (in 5-year age groups) and gender.

Eligible cases and controls were required to be English-speaking and to have a telephone number. We used several methods for obtaining telephone numbers including hiring companies specializing in locating individuals, manually searching publicly available databases, telephone books, and web sites, or sending a letter requesting a telephone number if these other methods were unsuccessful. Once we located a telephone number, we then sent a letter introducing the research study, followed by a telephone call to invite participation. Data collection began in December 2004 and was completed in March 2009.

Data collection and participation

After receiving a self-administered questionnaire, selected information was entered into a computer-assisted telephone interview system to facilitate a subsequent, detailed 1-hour telephone interview. A reference date was assigned to each participant. For cases, this date was the date of diagnosis, and for controls, this date was the date the invitation letter was sent less the mean time between cases' diagnosis and when cases were released to the study.

Exposure measurement

Because devices varied widely and no standardized instruments to measure exposure to tanning devices were available, we developed and pilot-tested a new tanning device instrument by first conducting in-depth interviews with seven individuals that had tanned indoors to identify device types, determine their common names, and find the best approach for collecting lifetime history of indoor tanning use. From this process, we developed a mixed mode instrument for collecting information about tanning devices used at various ages, which we tested with another 32 individuals. The final instrument, consisting of a self-administered questionnaire and telephone interview, was implemented in this study.

The self-administered portion of the tanning device instrument contained six columns with photographs for

each device: regular tanning beds/booths without facial lamps (variable ratios of UVB to UVA), regular tanning beds/booths with facial lamps (similar to devices without facial lamps; facial lamps are primarily UVA emitting), high-speed or high-intensity tanning beds/booths (UVB enhanced), high-pressure tanning beds/booths (primarily UVA emitting), sun lamps, or partial body tanners. Under each column, participants checked the age at which the device had been used, in 5-year age blocks from age 11 to age 59 (the oldest age at reference date). This information was then entered into the computer-assisted telephone interview system to guide device-specific questions during the telephone interview about use in each 5-year age period. These telephone-based questions included the number of years used within each 5-year age period, location of use (home, business, or other), and whether use was "occasional" or "fairly regular." If the participant was an occasional user, we asked about times per year of use, and if a fairly regular user, we asked about the number of months in which use occurred, and then times used per month. We also asked about the number of minutes of a typical session. We derived the specific years in which use occurred from birth year, year at reference age, age at tanning initiation, and age at tanning cessation. We calculated measures of ever use (based on reported age of initiation), dose (hours, sessions), and duration (years) across all devices, for specific devices, and for specific time periods. We classified regular beds/booths with and without facial lamps as conventional devices, and dropped partial tanners due to infrequent use. We also asked about frequency of burns attributed to an indoor tanning session or to sun after indoor tanning.

Other risk factors

We collected skin, hair and eye color, and presence and pattern of freckles and moles via the self-administered questionnaire. Education, income, family history of melanoma (diagnosed in parents, siblings, children, grandparents, grandchildren), all sun exposure measures, history and number of painful sunburns before and after age 18, and sunscreen use were collected during the telephone interview. Lifetime routine sun exposure was

Table 1. Outcome of recruitment of cases and controls (Skin Health Study)

	Cases	Controls
	n (%)	*n* (%)
Total from cancer registry (cases) or from drivers license list (controls)	2,026 (100.0)	3,095 (100.0)
Unable to determine eligibility		
Total	557 (27.5)	1,354 (43.7)
No phone available	164	598
Not reached by phone	71	273
Subject refused	79	468
Physician refusal	124	—
Died	23	15
Nonparticipating institution	93	—
Other	3	—
Respondent not eligible		
Total	89 (4.4)	151 (4.9)
Prior melanoma	76	14
Noncutaneous melanoma	2	—
Not melanoma	1	—
Not residing in Minnesota	0	63
Language/other	10	74
Respondents screened and eligible		
Total	1,380 (68.1)	1,590 (51.4)
Did not return self-administered questionnaire	186 (13.5)	447 (28.1)
Did not return	128	269
Refused	55	174
Died	2	1
Other	1	3
Did not complete telephone interview	27 (1.9)	42 (2.7)
Not reached	17	26
Refused/incomplete	9	14
Died/incapable	1	2
Completed self-administered questionnaire and telephone interview	1,167 (84.6)	1,101 (69.2)

Table 2. Comparison of cases and controls in the Skin Health Study

Characteristic	Cases *n* (%)	Controls *n* (%)	Crude OR (95% CI)
Age (y)			
25-29	76 (6.5)	68 (6.2)	1.03 (0.72-1.46)
30-39	198 (17.0)	193 (17.5)	0.94 (0.75-1.20)
40-49	407 (34.9)	393 (35.7)	0.95 (0.79-1.15)
50-59	486 (41.6)	447 (40.6)	1.00
Gender			
Male	468 (40.1)	445 (40.4)	0.99 (0.83-1.17)
Female	699 (59.9)	656 (59.6)	1.00
Income			
<$60,000	348 (29.8)	373 (33.9)	0.82 (0.69-0.98)
$60,000+	798 (68.4)	703 (63.9)	1.00
Missing	21 (1.8)	25 (2.2)	
Completed college			
No	612 (52.4)	610 (55.4)	0.88 (0.75-1.04)
Yes	555 (47.6)	489 (44.4)	1.00
Missing	0 (0.0)	2 (0.2)	
Eye color			
Gray/blue	529 (45.3)	445 (40.4)	1.46 (1.18-1.82)
Green	175 (15.0)	142 (12.9)	1.52 (1.14-2.01)
Hazel	237 (20.3)	236 (21.4)	1.24 (0.96-1.59)
Brown	226 (19.4)	278 (25.3)	1.00
Natural hair color			
Red	120 (10.3)	46 (4.2)	3.53 (2.43-5.12)
Blonde	362 (31.0)	226 (20.5)	2.17 (1.73-2.72)
Light brown	396 (33.9)	438 (39.8)	1.22 (1.00-1.50)
Dark brown/black	289 (24.8)	391 (35.5)	1.00
Skin color (inside upper arm)			
Very fair	215 (18.4)	128 (11.6)	5.50 (2.70-11.18)
Fair	827 (70.9)	746 (67.8)	3.63 (1.83-7.18)
Light olive	114 (9.8)	191 (17.4)	1.95 (0.96-3.99)
Dark olive, brown, black	11 (0.9)	36 (3.2)	1.00
Moles			
Many	71 (6.1)	12 (1.1)	13.81 (7.32-26.05)
Some	250 (21.4)	92 (8.4)	6.35 (4.73-8.51)
Few	644 (55.2)	545 (49.5)	2.76 (2.25-3.39)
None	191 (16.4)	446 (40.5)	1.00
Missing	11 (0.9)	6 (0.5)	
Freckles			
Many	18 (1.6)	11 (1.0)	1.90 (0.89-4.06)
Some	75 (6.4)	44 (4.0)	1.98 (1.34-2.92)
Few	196 (16.8)	127 (11.5)	1.79 (1.39-2.30)
Very few	326 (27.9)	278 (25.3)	1.36 (1.12-1.66)
None	547 (46.9)	635 (57.7)	1.0
Missing	5 (0.4)	6 (0.5)	
Family history of melanoma			
Yes	216 (18.5)	224 (20.3)	0.87 (0.71-1.08)
No	939 (80.5)	850 (77.2)	1.00
Missing	12 (1.0)	27 (2.5)	

(*Continued on the following page*)

Table 2. Comparison of cases and controls in the Skin Health Study (Cont'd)

Characteristic	Cases *n* (%)	Controls *n* (%)	Crude OR (95% CI)
Lifetime routine sun exposure (h)			
High	372 (31.9)	382 (34.7)	0.85 (0.70-1.05)
Medium	390 (33.4)	365 (33.1)	0.94 (0.77-1.15)
Low	399 (34.2)	350 (31.8)	1.00
Missing	6 (0.5)	4 (0.4)	
Lifetime sun exposure from outdoor activities (h)			
High	388 (33.2)	367 (33.3)	0.95 (0.78-1.16)
Medium	378 (32.4)	377 (34.2)	0.90 (0.74-1.10)
Low	397 (34.0)	357 (32.5)	1.00
Missing	4 (0.4)	0 (0.0)	
Lifetime sun exposure from outdoor jobs (h)			
High	210 (18.0)	232 (21.1)	0.84 (0.68-1.04)
Low	262 (22.5)	225 (20.4)	1.08 (0.88-1.33)
None	689 (59.0)	640 (58.1)	1.00
Missing	6 (0.5)	4 (0.4)	
Mean lifetime sunscreen use			
High	405 (34.7)	351 (31.9)	1.31 (1.07-1.61)
Medium	409 (35.0)	349 (31.7)	1.34 (1.09-1.63)
Low	352 (30.2)	401 (36.4)	1.00
Missing	1 (0.1)	0 (0.0)	
Lifetime number of burns from sun (lasting more than 1 d)			
>5	739 (63.3)	595 (54.0)	2.56 (1.67-3.93)
3-5	224 (19.2)	215 (19.5)	2.15 (1.36-3.39)
1-2	168 (14.4)	221 (20.0)	1.57 (0.99-2.49)
None	33 (2.8)	68 (6.3)	1.00
Missing	3 (0.3)	2 (0.2)	

obtained by multiplying the number of days by the number of hours typically spent outside on weekdays and weekends during winter and summer months in the decade years (at age 10, 20, 30, 40, and 50, depending on a person's age), and summing across decades. This instrument was developed by Kricker et al. and found to be reliable and well correlated with skin damage (46-49). Sun exposure during outdoor activities was based on a list of 11 outdoor activities in which the participant had engaged for at least 4 days per year in the decade years. The outdoor activities included time spent at the beach or pool, sunbathing, boating or water-skiing, fishing, playing or coaching outdoor team sports, walking, hiking or jogging, biking, roller skating or rollerblading, golfing, playing tennis, playing outside, and gardening. The total number of days spent in each activity was multiplied by the number of hours for each activity, and summed across activities and decades. We also asked about total hours of sun exposure associated with all outdoor jobs during warmer and cooler months and calculated total hours in a manner similar to total hours for routine and outdoor activity sun exposure. Lifetime sunscreen use was measured by averaging the frequency of sunscreen use (almost always, more than half the time, about half the time, less than half the time, rarely, never) associated with each outdoor activity reported in each decade year.

Assessment of bias

Due to challenges in recruiting controls, we implemented procedures in July 2007 to assess potential for selection bias. Among persons that refused participation at the first recruitment call (excluding persons explicit about no further contact or that we had been unsuccessful in reaching), we randomly selected cases and controls to re-contact and ask six questions. The questions included past use of indoor tanning ("have you ever tanned indoors?"), total number of sessions if used, number of lifetime sunburns, skin sensitivity to sun, sunscreen use, and income. We also attempted to re-contact and query all cases and controls that had not returned the self-administered questionnaire by this point. Going forward, we then asked these questions of all persons during routine reminder calls to return the self-administered questionnaire. Altogether, we obtained this information from 32% of cases and 15% of controls among all nonparticipants.

Table 3. The association between indoor tanning history with melanoma risk (Skin Health Study)

Indoor tanning	Cases	Controls	Age- and gender-adjusted OR (95% CI)	Multivariate adjusted OR* (95% CI)
	n (%)	*n* (%)		
Never used	433 (37.1)	538 (48.9)	1.00	1.00
Ever used	734 (62.9)	563 (51.1)	1.81 (1.51-2.21)	1.74 (1.42-2.14)
Frequency of use (h)				
1-9	322 (27.6)	289 (26.2)	1.58 (1.28-1.96)	1.46 (1.15-1.85)
10-19	74 (6.3)	66 (6.0)	1.62 (1.12-2.34)	1.81 (1.21-2.70)
20-49	129 (11.1)	90 (8.2)	2.10 (1.53-2.88)	2.18 (1.54-3.08)
50+	200 (17.1)	95 (8.6)	3.27 (2.42-4.41)	3.18 (2.28-4.43)
P trend			<0.0001	<0.0001
Frequency of use, sessions				
≤10	149 (12.8)	141 (12.8)	1.47 (1.12-1.93)	1.34 (1.00-1.81)
11-24	130 (11.1)	100 (9.1)	1.84 (1.36-2.48)	1.80 (1.30-2.49)
25-100	173 (14.8)	147 (13.4)	1.71 (1.30-2.23)	1.68 (1.25-2.26)
>100	275 (23.6)	154 (14.0)	2.71 (2.08-3.51)	2.72 (2.04-3.63)
P trend			0.0005	0.0002
Age at initiation (y)				
<18	209 (17.9)	161 (14.6)	2.18 (1.62-2.94)	1.85 (1.33-2.57)
18-24	175 (15.0)	125 (11.4)	2.14 (1.60-2.85)	1.91 (1.39-2.62)
25-34	150 (12.9)	143 (13.0)	1.43 (1.09-1,87)	1.46 (1.09-1.97)
35+	199 (17.1)	134 (12.1)	1.79 (1.38-2.33)	1.83 (1.37-2.43)
P trend			0.37	0.68
Duration of use (y)				
1	123 (10.5)	110 (10.0)	1.52 (1.13-2.03)	1.47 (1.06-2.02)
2-5	236 (20.2)	194 (17.6)	1.74 (1.36-2.21)	1.64 (1.26-2.15)
6-9	124 (10.6)	95 (8.6)	1.93 (1.41-2.64)	1.85 (1.31-2.61)
10+	245 (21.0)	146 (13.3)	2.47 (1.90-3.21)	2.45 (1.83-3.28)
P trend			0.0036	0.006
Burns from indoor tanning				
No	476 (40.8)	410 (37.2)	1.60 (1.32-1.95)	1.59 (1.28-1.97)
Yes	258 (22.1)	153 (13.9)	2.60 (2.00-3.39)	2.28 (1.71-3.04)
Number of times burned, indoor tanning				
1	62 (5.3)	37 (3.4)	2.46 (1.59-3.82)	2.40 (1.49-3.87)
2	53 (4.5)	41 (3.7)	1.99 (1.28-3.10)	1.83 (1.13-2.99)
3-5	70 (6.0)	46 (4.2)	2.42 (1.60-3.66)	2.05 (1.31-3.20)
>5	72 (6.2)	29 (2.6)	4.04 (2.52-6.49)	3.12 (1.86-5.23)
P trend			0.0001	0.01
Burns from sun after indoor tanning				
No	536 (45.9)	435 (39.5)	1.71 (1.41-2.08)	1.67 (1.35-2.07)
Yes	195 (16.7)	127 (11.5)	2.19 (1.67-2.88)	2.00 (1.48-2.70)

NOTE: Frequency totals for indoor tanning measures might not add up to 100% due to missing values.
*Adjusted for age, gender, eye color, natural hair color, skin color, freckles, moles, income, education, family history of melanoma, routine sun exposure, outdoor activity sun exposure, outdoor job exposure, mean sunscreen use, and number of lifetime painful sunburns; an additional 16 cases and 12 controls were excluded because the number of missing values was too small to be included as its own category.

We also assessed recall bias possibly introduced by physicians revealing the study hypothesis to their patients prior to permitting the release of names. So, beginning in May 2008, we asked each participant at the end of the telephone interview (12.9% and 17.3% of all interviewed cases and controls, respectively) if they had talked to a physician about the study before we first made contact with them.

Statistical analysis

Using multiple logistic regression, we calculated odds ratios (OR) and 95% confidence intervals (CI) for the

likelihood of melanoma associated with having ever tanned indoors, frequency of use (total hours, sessions, or years), age of initiation, and burns from indoor tanning or sun after indoor tanning. Total hours, sessions, or years were divided into categories comparable with other reports. For these measures, a P value for trend was calculated by treating the categories as ordinal. We compared cases to controls according to the types of indoor tanning devices used and period of use, i.e., before 1990, 1990 or later, or in both periods. The year 1990 was chosen to identify the time period when high-speed/high-intensity and high-pressure devices became more widely available. We also examined use according to tumor location (head and neck, trunk, upper or lower limbs) and gender. All analyses were first adjusted for age at reference date (in years) and gender (if not stratified on this characteristic). In multivariate analyses, ORs and 95% CIs were also adjusted for income (≤$60,000, >$60,000, missing), education (completed college, did not complete college), eye color (gray/blue, green, hazel, or brown), hair color (red, blond, light brown, or dark brown/black), skin color (very fair, fair, light olive versus dark olive, brown, very dark brown, or black), freckles (none, very few, few, some, many, missing), moles (none, few, some, many, missing), family history of melanoma (yes or no, missing), total lifetime painful sunburns lasting more than 1 day (continuous), routine sun exposure (continuous), sun exposure from outdoor activities (continuous), sun exposure from outdoor jobs (continuous), and lifetime sunscreen use (continuous). A total of 16 cases and 12 controls were excluded because of missing data for one or more confounders.

To examine whether indoor tanning exposure initiated at a young age reflected higher cumulative exposure or biological susceptibility among younger persons, we examined age of initiation and duration of use simultaneously (among indoor tanners only), while adjusting for previously mentioned confounders. Similarly, we examined the period of use while controlling for total number of years used to determine whether or not exposure to earlier devices conferred greater risk than later devices, independent of total years of exposure. We compared users relative to nonusers (never tanners, plus nonusers of a specific device) of conventional, high-speed/high-intensity, and high-pressure devices in the same model to assess whether each device contributed independently to melanoma risk. We allowed for latency by estimating the likelihood of melanoma associated with indoor tanning use by stratifying according to use initiated more than or less than 15 years from the reference date. Associations between indoor tanning use and melanoma were examined by tumor characteristics (tumor site, Breslow's depth, presence of ulceration, or histologic subtype) and tested for statistically significant differences by age at diagnosis, gender, and phenotypic characteristics. Finding no evidence that results were modified by these characteristics (e.g., P for interaction by phenotypic characteristics ranged from 0.37 to 0.76), we present results for all cases and controls.

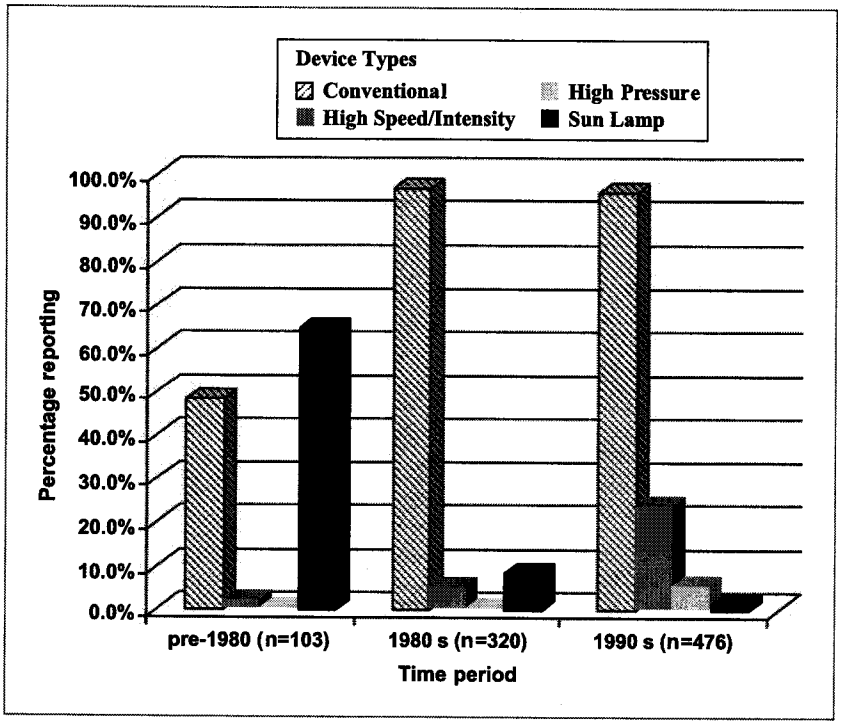

Figure 1. Tanning device use by time period among 563 controls (Skin Health Study).

Results

Eligibility was determined for 72.5% of cases and 56.3% of controls (Table 1). Among known eligible cases and controls, 1,167 cases (84.6%) and 1,101 controls (69.2%) completed the self-administered questionnaire and telephone interview between December 2004 and March 2009. Due to frequency matching, cases and controls had similar age and gender distributions (Table 2); 98% of cases and 96% of controls were Caucasian. Phenotypic characteristics known to increase melanoma risk and greater number of sunburns were more common among cases than controls. For sun exposure, we observed no association with case-control status whether we assessed sun exposure from routine, outdoor recreational activities or occupational lifetime exposure. History of sunscreen use was reported more frequently by cases than controls in the crude analysis.

Indoor tanning use was reported by 62.9% of cases and 51.1% of controls (Table 3). Because age- and gender-adjusted ORs varied only slightly from multivariate-adjusted ORs, the latter are described throughout. The multivariate-adjusted OR for the likelihood of melanoma in relation to having ever tanned indoors was 1.74 (95% CI, 1.42-2.14) and confidence intervals excluded the null value. Melanoma risk increased markedly with frequency of use. Adjusted ORs ranged between approximately 2.5 and 3.0 for the highest category of use—50+ hours, more than 100 sessions, 10 or more years—and the P for trend was 0.006 to <0.0001, depending on the measure. A significant trend in the likelihood of melanoma with increasing number of sessions was also observed for melanomas arising on each tumor site (data not shown). When examined by gender, this dose-response pattern held for both men ($P < 0.0001$) and women ($P < 0.0001$) with melanoma arising on the trunk, among men with melanoma on the head and neck ($P = 0.05$), and among women diagnosed with melanoma on the upper ($P = 0.006$) or lower limbs ($P < 0.0001$). Cases were also more likely than controls to report having experienced painful burns from indoor tanning (adjusted OR, 2.28; 95% CI, 1.71-3.04), a greater number of indoor tanning-related burns (P trend = 0.01), or painful sunburns at a time when they thought they were protected from the sun by indoor tanning (adjusted OR, 2.00; 95% CI, 1.48-2.70).

Adjusted ORs for the likelihood of melanoma among users of indoor tanning relative to never users were similarly elevated regardless of the age when indoor tanning began (Table 3; P trend = 0.68). When we restricted the analysis to indoor tanners and simultaneously modeled age of initiation and total years used, ORs were attenuated for each category of age at which use began or according to number of years, but the significant trend associated with duration remained (data not shown). After accounting for age at initiation among indoor tanners, the risk of melanoma was concentrated among users for 10 or more years compared with users for only 1 year (adjusted OR, 1.77; 95% CI, 1.19-2.63).

Table 4. Association between indoor tanning device types and period of indoor tanning use and the likelihood of melanoma (Skin Health Study)

Indoor tanning	Cases	Controls	Age- and gender-adjusted OR (95% CI)	Multivariate adjusted OR* (95% CI)
	n (%)	*n* (%)		
Never used	433 (37.1)	538 (48.9)	1.00	1.00
Ever used device				
Conventional	697 (59.7)	535 (48.6)	1.83 (1.51-2.21)	1.76 (1.43-2.17)
High speed/high intensity	200 (17.1)	118 (10.7)	2.72 (1.99-3.70)	2.86 (2.03-4.03)
High pressure	55 (4.7)	25 (2.3)	3.79 (2.22-6.49)	4.44 (2.45-8.02)
Sun lamp	108 (9.3)	79 (7.2)	1.88 (1.34-2.63)	1.85 (1.27-2.70)
Periods of use				
Before 1990	135 (11.6)	96 (8.7)	1.85 (1.37-2.49)	1.63 (1.18-2.27)
After 1990	269 (23.1)	223 (20.3)	1.72 (1.36-2.19)	1.78 (1.37-2.32)
Both periods	327 (28.0)	235 (21.3)	1.94 (1.55-2.44)	1.83 (1.42-2.36)
Adjusted for no. of years used				
Before 1990			1.76 (1.30-2.38)	1.53 (1.09-2.13)
After 1990			1.51 (1.61-1.95)	1.51 (1.14-2.01)
Both periods			1.33 (0.96-1.84)	1.15 (0.81-1.64)

NOTE: Frequency totals for indoor tanning measures might not add up to 100% due to missing values.
*Adjusted for age, gender, eye color, natural hair color, skin color, freckles, moles, income, education, family history of melanoma, routine sun exposure, outdoor activity sun exposure, outdoor job exposure, mean sunscreen use, and number of lifetime painful sunburns; an additional 16 cases and 12 controls were excluded because the number of missing values was too small to be included as its own category.

Table 5. Association between indoor tanning and risk of melanoma by possible recall and selection bias among cases and controls (Skin Health Study)

Observed	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)*
All participants				
n	1,167	1,101		
% ever tanned indoors	62.9	51.1	1.62 (1.37-1.92)	1.74 (1.42-2.14)
Evaluation of recall bias				
Participants who talked with their physician†				
n	21	3		
% ever tanned indoors	71.4	66.7	1.25 (0.10-16.50)	—‡
Participants who did not talk with their physician				
n	130	188		
% ever tanned indoors	57.7	52.7	1.23 (0.78-1.92)	1.72 (0.92-3.22)
Evaluation of selection bias				
Nonparticipants who answered brief questionnaire				
n	107	180		
% ever tanned indoors	60.8	48.3	1.62 (1.00-3.61)	—§

*Adjusted for age, gender, eye color, natural hair color, skin color, freckles, moles, income, education, family history of melanoma, routine sun exposure, outdoor activity sun exposure, outdoor job exposure, mean sunscreen use, and number of lifetime painful sunburns; analysis among all participants excludes an additional 16 cases and 12 controls because the number of missing values was too small to be included as its own category. Analysis of recall bias excludes only two additional cases and three controls for the same reason.

†Excludes nine cases and three controls who responded "don't know" or whose response was missing.

‡Not possible to estimate due to small numbers.

§Confounders not collected on nonparticipants.

Controls reported use of different types of devices that generally coincided with their availability over time (Fig. 1); cases were more likely than controls to report use of each type of device shown. The likelihood of melanoma was significantly increased 2.86 and 4.44 times for users of high-speed/high-intensity devices and high-pressure devices, respectively; and 1.76 and 1.85 times for users of conventional devices and sunlamps, respectively, relative to never users (Table 4). When the reference group was changed to be nonusers of a specific device (as opposed to never users), the associations were attenuated, ranging from 1.6 to 1.9 depending on the device, yet confidence intervals for each estimate still excluded 1.0 (data not shown). The risk of melanoma was elevated for use occurring before or after 1990, or in both periods (Table 4). After accounting for the number of years of indoor tanning use in each period, these associations persisted except among cases and controls that reported use in both periods. The associations by device type, dose and duration were similar whether use was initiated at least 15 years prior to or within 15 years of the reference date (data not shown).

Crude ORs for the likelihood of melanoma among past compared with never users of indoor tanning were similar for participants and nonparticipants (Table 5). Among cases and controls that did and did not report speaking with a physician, crude ORs were each ~1.2, weaker than what was observed among all study participants. However, multivariate adjustment resulted in an OR of 1.72 among cases and controls that said they did not speak to their physician before enrolling in the study, similar to the overall point estimate of 1.74. The small number of cases and controls that reported speaking to their physician precluded calculation of an adjusted OR in this group.

Discussion

Our study has several important findings. First, we found that melanoma occurred more frequently among indoor tanners compared with persons that never engaged in this activity. Second, we found a strong dose-response relationship between melanoma risk measured by total hours, sessions, or years. Furthermore, this dose-response was also seen for melanomas arising on the trunk, not only in men but also in women, that would not ordinarily expose this site to UV radiation except when tanning or sunbathing. Third, we found an increased risk of melanoma with use of each type of tanning device as well as with each period of tanning use, suggesting that no device could be considered "safe." In addition, burns from indoor tanning seemed to be fairly common and conferred a similar risk of melanoma to sunburns. These associations remained significant even after

adjusting for the potential confounding effects of known risk factors for melanoma.

We did not confirm the IARC report's emphasis on an increased risk of melanoma with first exposure to indoor tanning "in youth", defined as use before the age of 36 (5). Except for one cohort and two case-control studies that examined indoor tanning during adolescence in relation to melanoma (30-32), all other reports considered use prior to ages 25 to 30 (11, 17, 21), or restricted the analysis to cases diagnosed before the age of 36 (22, 28). This restriction, however, could have resulted in the exclusion of older cases and controls that may have been exposed at a younger age. An elevated risk of melanoma associated with first use at younger ages has been consistently observed across these studies, but this is also the case for indoor tanning used at older ages in some reports reviewed by the IARC (11, 17, 22, 28, 31). Our study was designed to specifically evaluate indoor tanning use initiated at any age. And by simultaneously accounting for duration of use among indoor tanners, our analysis indicates that early age exposure is most likely a marker for cumulative exposure, the reason for an excess risk of melanoma, not that younger individuals are at increased susceptibility to the effects of UV radiation. Although no other study has analyzed these data in the same manner as we did, three reports provide further support for our observation. One recent report found total hours of sunbed exposure to be much higher (34 versus 9 hours) among persons that first tanned indoors before compared with after age 15 years (32). And in two studies that stratified frequency of indoor tanning use by age of cases, elevated risks for melanoma were observed for those with 10 or more sessions, regardless of age (22), or for those with regular use up to the age of 60 (28).

With our carefully designed questionnaire eliciting the use of specific devices that emit differing amounts of UVB and UVA, we observed considerably stronger ORs for melanoma among users of high-speed or high-pressure devices than among users of conventional devices. We still cannot be certain, however, that these results reflect higher exposure to UVB from high-speed devices or higher exposure to UVA from high-pressure devices. First, the proportion of subjects reporting use of these devices was quite low. Second, studies have shown that the percentage of UVB and UVA emitted depends on the type of lamp, the quality of maintenance, and the level of degradation—information that cannot be collected through retrospective recall (50-53). Recently, inspections of tanning devices in European tanning salons have revealed poor compliance with regulations for the allowable distribution of UVB versus UVA, with a concomitant increase in the proportion of UVB beyond permissible limits over time (54-56). If UVA is carcinogenic in humans, as stated in the IARC report, our findings are biologically plausible. However, it is also possible that the devices we assessed, regardless of our classification scheme, emitted sufficient UVB for that component of UV radiation to be the reason for the observed associations. Similar to our experience, other studies that collected information about device types have not been able to single out any one type as being higher risk than another (21, 27, 30, 32). Nor have most studies, ours included, found higher risks of melanoma associated with indoor tanning exposure in a specific period, despite changes in emission of UV components over time (21, 23, 30, 57). Although disentangling which wavelength is responsible for melanoma development might not be possible in epidemiologic studies, the evidence also indicates that all indoor tanning devices are harmful.

We did not find lifetime routine sun exposure or sun exposure via recreational outdoor activities or occupations to be associated with melanoma risk, nor were these results changed by a detailed examination of sun exposure according to season, decade age, type of outdoor activity, indoor tanning status, or tumor site. Indeed, published studies reveal that the relationship between sun exposure and melanoma is complex, and depends on whether the exposure is intermittent or chronic; inconsistencies in its measurement further complicates an understanding of these relationships. A meta-analysis of 57 studies (58) and a pooled analysis of 15 studies (59) each reported fairly weak associations between total sun exposure and melanoma, no relationship to chronic exposure (based on outdoor occupations), moderately strong associations with intermittent exposure (usually defined as sunbathing, time spent during sunny vacations, or outdoor recreational activities), and strong associations with sunburn. Thus, our results are in agreement with these reports for chronic exposure and sunburns. To the extent that sunburns are a marker of intermittent sun exposure, then our results adequately represent the independent effect of indoor tanning use on the risk of melanoma. Differential underreporting of sun exposure by cases seems to be a less likely explanation of these trends in our study; had it been operative, we might have expected the same to occur for cases' report of artificial solar exposure. Although our findings could reflect less variation in sun exposure among a relatively homogenous population residing in Minnesota, or the younger age of our study sample in contrast with most case-control studies of melanoma, we cannot exclude the possibility that nondifferential misclassification obscured a relationship between sun exposure and melanoma.

Although the prevalence of indoor tanning among participating controls (51.1%) is high compared with most other reports, we do not think this is due to differential selection of indoor tanners into the study. In a 2002 Minnesota statewide survey of adults, age 18 and older (37), we found that overall, 36.3% of respondents reported indoor tanning use; prevalence was higher (42%) in the sample with the same age range as the current study. More importantly, the frequency of indoor tanning use was very similar when we compared participating and nonparticipating cases and controls and crude ORs for the association between indoor tanning use and melanoma were identical for participants and

nonparticipants. We were also concerned that cases that had discussed the study with their physician might have reported higher frequency of indoor tanning use than cases that did not. We attempted to address this potential bias by querying both cases and controls in the latter part of the study. The fact that several controls (whose physicians were not contacted) reported discussions with their physician about the study prior to participating is also interesting. As the prevalence of overreporting was similar for both cases and controls in this group, and the adjusted OR among cases and controls that did not speak with a physician was similar to what we reported for the entire sample, recall bias seems less likely to explain our results. This conclusion is further supported by a recent nested case-control study, which reported no consistent pattern of recall bias for indoor tanning or other melanoma risk factors (60).

In summary, our study provides strong evidence that indoor tanning is a risk factor for melanoma. Due to the strength of the association, the dose-response, the results by tumor site (especially the trunk), and the ability to account for known confounders, our results address several limitations of previous studies. Our results also indicate that the number of times an individual is exposed to indoor tanning is more important than exposure to indoor tanning at an early age. Our ancillary studies on bias, although limited in scope, suggest that our results are not explained by selection or recall bias. In conclusion, our results add considerable weight to the IARC report that indoor tanning is carcinogenic in humans and should be avoided to reduce the risk of melanoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

American Cancer Society (RSGPB-04-083-01-CCE) and the National Cancer Institute (5R01CA106807).

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Received 12/04/2009; revised 02/09/2010; accepted 02/25/2010; published OnlineFirst 05/27/2010.

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Int. J. Cancer: **120,** 1116–1122 (2006)

The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review

The International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer

Exposure to solar ultraviolet (UV) radiation is a known cause of skin cancer. Sunbed use represents an increasingly frequent source of artificial UV exposure in light-skinned populations. To assess the available evidence of the association between sunbed use and cutaneous malignant melanoma (melanoma) and other skin cancers, a systematic review of the literature till March 2006 on epidemiological and biological studies on sunbed use was performed in Pubmed, ISI Web of Science, Embase, Pascal, Cochrane library, Lilacs and Medcarib. Search for keywords in the title and in the abstract was done systematically and supplemented by manual searches. Only case–control, cohort or cross-sectional studies were selected. Data were abstracted by means of a standardized data-collection protocol. Based on 19 informative studies, ever-use of sunbeds was positively associated with melanoma (summary relative risk, 1.15; 95% CI, 1.00–1.31), although there was no consistent evidence of a dose–response relationship. First exposure to sunbeds before 35 years of age significantly increased the risk of melanoma, based on 7 informative studies (summary relative risk, 1.75; 95% CI, 1.35–2.26). The summary relative risk of 3 studies of squamous cell carcinoma showed an increased risk. For basal cell carcinoma, the studies did not support an association. The evidence does not support a protective effect of the use of sunbeds against damage to the skin from subsequent sun exposure. Young adults should be discouraged from using indoor tanning equipment and restricted access to sunbeds by minors should be strongly considered.

Key words: artificial UV; sunbeds; melanoma; skin cancer; meta-analysis

Sun exposure is the main environmental cause of skin cancer, and ultraviolet (UV) radiation is the solar wavelength involved in skin cancer, including the malignant cutaneous melanoma.[1] People may also be exposed to UV radiation through many artificial sources at home and in the workplace, with some individuals receiving high doses. Sources of artificial UV radiation include various lamps used in medicine, industry, business and research, as well as for domestic and cosmetic purposes. Sunbeds and sunlamps used for tanning purposes are the main source of deliberate exposure to artificial UV radiation.[†] Although the contexts of sun exposure and indoor tanning differ, both deliver UV radiation, and their health effects would therefore be expected to be similar.

UV radiation wavelengths range between 100 and 400 nm and are broadly categorized into UVA (>315–400 nm), UVB (>280–315 nm) and UVC (100–280 nm). Modern indoor tanning equipment mainly emits in the UVA range, but a fraction (*i.e.*, <5%) of this spectrum is in the UVB range.

Before 1990, UVB was usually considered the only carcinogenic part of the solar spectrum, but since then UVA as well has been suspected of having carcinogenic potential. In 1992, the International Agency for Research on Cancer (IARC) classified UVB and UVA radiation, as well as "use of sunlamps and sunbeds," as "probably carcinogenic to humans" (Group 2A of the IARC classification of carcinogenic agents).[1] More recently, the 10th Report on Carcinogens published by the National Toxicology Program in the USA classified UVA radiation as a "known to be a human carcinogen."[2] Biological mechanisms by which chronic sun exposure causes squamous cell cancer (SCC) of the skin have become better known and chronic exposure to high UVB doses is now considered as the main environmental cause of that skin cancer.[3] Biological mechanisms implicated in basal cell carcinoma (BCC) start to be better known. In contrast, we still have poor knowledge of the UV wavelength and the dose delivery pattern at skin level implicated in the genesis of melanoma and of BCC.[4]

Indoor tanning is widely practiced in most developed countries, particularly in Northern Europe and the USA, and is gaining popularity even in sunny countries such as Australia.[5,6] The likely impact of this fashion on skin cancer incidence is of substantial concern, mainly for cutaneous malignant melanoma (hereafter melanoma), a cancer of poor prognosis when diagnosed at an advanced stage.

This paper summarizes a systematic review of epidemiological and experimental studies on use of indoor tanning equipment and skin cancer developed by a Working Group convened by IARC.

UV spectra from sunlight and indoor UV tanning appliances

During a sunny day on the Mediterranean coast, the solar UV spectrum at noon contains 4–5% UVB and 95–96% UVA. When UV output of a typical indoor tanning appliance is calculated in terms of biological activity, as estimated by the erythema-effective irradiance, the emission of many tanning appliances is equivalent to or exceeds the emission of the midday sun in southern Europe.[7,8] The UV intensity of powerful tanning appliances may be 10–15 times higher than that of the midday sun,[8] leading to UVA doses per unit of time received by the skin during a typical tanning session that are well above those experienced during ordinary daily activities or even during sunbathing. As a result, the annual UVA doses received by frequent indoor tanners may be 1.2–4.7 times those received from the sun, in addition to those received from the sun.[9] This widespread repeated exposure to high doses of UVA constitutes a new phenomenon for human beings.

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[†]The device used for tanning may be referred to as sunbed, sunlamp, artificial UV, artificial light or tanning bed, among other terms. Also, a number of terms are used to define a place where indoor tanning may occur: solarium, tanning salon, tanning parlor, tanning booth, indoor tanning salon, indoor tanning facility. In addition, indoor tanning may also occur in non-commercial premises. For the purpose of this report, the term *indoor tanning equipment* has been used throughout.

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Received 8 June 2006; Accepted after revision 27 September 2006
DOI 10.1002/ijc.22453
Published online 27 November 2006 in Wiley InterScience (www.interscience.wiley.com).

In the 1990s, regulations in some countries (*e.g.*, France, Sweden) limited to 1.5% the maximum percentage of UVB in the UV output of tanning appliances. However, in practice, the UV output and spectral characteristics (*i.e.*, amounts of UVA, UVB, visible light and infrared radiation) of tanning appliances vary considerably. The proportion of UVB in UV energy output could vary from 0.5 to 4%,[10,11] and may attain an emission spectrum similar to the sun spectrum in the UVB range.[8] These differences are due to sunbed design (*e.g.*, the numbers and type of fluorescent tubes, the presence of high pressure UV lamps, the materials composing filters, the distance from canopy to the skin), sunbed power and tube ageing.

Biological effects of exposure to artificial UV radiation relevant to carcinogenesis

A large body of experimental and epidemiological data strongly indicates that the spectrum of UV radiation reaching the Earth's surface causes skin cancer.[1,12,13] UVB is a complete carcinogen that is absorbed by DNA and can damage DNA directly.[13]

Evidence of the mutagenic properties of UVA in humans has been found in several studies.[12–14] UVA radiation does cause UVB-like cyclobutane pyrimidine dimers and 6-4 photoproducts, albeit with a much lower efficacy than does UVB radiation. Most of the DNA damage induced by UVA is indirect, through the absorption of UVA photons by other cellular structures (chromophores), with formation of reactive oxygen species that can transfer UVA energy to DNA *via* mutagenic oxidative intermediates.[15]

Skin of human volunteers exposed to UVA lamps used in tanning appliances show DNA damage, *p53* mutations induced by oxidative damage and alterations of the p53 protein similar to those observed after sun exposure or after exposure of experimental animals.[16–18]

UVA penetrates deeper into human skin than does UVB. Because UVA represents the largest proportion of the UV spectrum of tanning appliances and of solar radiation reaching the Earth's surface, far more UVA than UVB reaches the basal layers of the epidermis where melanocytes and early keratinocytic cells are located.

Both UVA and UVB radiation can affect the immune response that may be involved in the promotion of melanoma,[15,19,20] but the 2 types of radiation seem to act differently.[21,22] UVB induces immunosuppression at both the local and systemic levels, while UVA does not induce systemic immune suppression.[23]

To date, evidence obtained from experimental studies on the involvement of high UVB doses in the causation of SCC is consistent with observations in humans. In contrast, experimental studies give conflicting results regarding the roles of UVB and UVA in the induction of melanoma in humans. The same uncertainties hold true for BCC, a type of tumor that shares some epidemiological characteristics of melanoma.

Experiments carried out in animals cannot reproduce the complex interplay in individuals between highly variable natural susceptibilities to UV radiation, sun exposure behaviors and exposure to various sources of UV radiation. During indoor tanning, such interrelationships may be critical, as users are more inclined than the average population to engage in outdoor tanning activities,[24] and indoor tanning sessions often precede or follow active sun exposure or outdoor tanning.

Effects of artificial UV on human skin

Skin redness or burning are reported by 18–55% of users of indoor tanning equipment in Europe and North America.[25] Although UVB is far more potent than UVA in causing sunburn, high fluxes of UVA are capable of inducing skin redness in individuals sensitive to sunlight or with only moderate tanning ability.

In individuals who tan easily, exposure to tanning appliances will lead first to the oxidation of melanin already present in superficial keratinocytic layers of the skin, known as immediate pigment darkening.[26] A more permanent tan is acquired with accumulation of exposure, depending on tanning ability and on the amount of UVB present in the UV spectrum of the lamps.

Immediate pigment darkening has no photoprotective effect against UV-induced skin redness or sunburn.[27] Moreover a UVA-induced permanent tan provides little photoprotection[28,29] and the skin thickening caused by UVA affords only very little photoprotection.[30] Studies in humans show that a prevacation tan induced artificially offers virtually no protection against sun-induced DNA damage.[31–33]

Exposure to artificial UV for tanning purposes

Few people had used indoor tanning equipment before 1980 but by the end of the 1990s more than 60% of women and 50% of men aged 18–50 years in Northern Europe reported having ever used indoor tanning equipment.[34] Indeed, prevalence of indoor tanning is increasing so rapidly in many countries that current estimates may be outdated rapidly. The most frequent motivations for indoor tanning are the acquisition of a so-called safe tan and preparation of the skin before sun exposure.[25]

Use of indoor tanning equipment is more prevalent among women and among both men and women younger than 35 years. Earliest studies in Sweden and in the USA tended to find indoor tanning to be more prevalent among adolescents with fair skin types who are more prone to sunburn.[35–37] More recent studies in the USA found either the opposite[38–40] or no association.[41]

Few studies have assessed the compliance of indoor tanning facility operators or consumers with recommendations and regulations. Overall, information provided by tanning salon operators on health risks and on duration and frequency of exposure is often incomplete, and there is a lack of identification of highly sun-sensitive subjects or of subjects taking photosensitizing medications.[6,42–44]

About 17–35% sunbed users reported that they did not wear eye protection.[10,41,43] In some surveys, 16% of sunbed users may have had more than 100 sessions per year,[10] and most users tend to exceed the recommended exposure times.[41,44,45]

Since 1989, a total of 16 studies (18 reports) have examined prevalence of indoor tanning among children and adolescents aged 8–19 years in Australia, Europe and the USA.[46,47] All studies showed a frequent use by adolescents and children, sometimes at a very young age. According to the most recent studies, 30% of adolescents in Sweden and 24% of adolescents in the USA aged 13–19 years reported ever-use of indoor tanning equipment and 8 and 12% respectively were frequent users (10 times per year or more). In a recent survey in the United Kingdom, while 7% of children aged 8–11 years reported exposure to a sunbed in the past 6 months, as many as 48% expressed a desire to use a sunbed.[48]

Epidemiological studies on indoor tanning and skin cancer

As existing animal models of human melanoma are inconsistent, evidence of an association between indoor tanning and skin cancer must be sought predominantly from epidemiological studies. Few studies have addressed this topic specifically, but some studies included 1 or more secondary questions about indoor tanning. We systematically analyzed the results from the relevant studies and compiled them in a metaanalysis.

Methods

The methodology used for the literature search is summarized in Table I. The minimal common information about exposure to indoor tanning appliances for all studies was "ever exposed." For those studies wherein "ever exposed to indoor tanning appliances *versus* never" was not strictly assessed[49,50] we used the information closest to this category.

Most estimates included all subjects and combined sexes in the analysis. Some studies presented results separately for women and men, with no combined data, in which case both estimates were

included. Since the studies used different age categories for classifying age at first exposure, we considered as "young exposure" those exposures that started before 35 years of age.

Every measure of association adjusted for the maximum number of confounding variables, and corresponding confidence interval (CI), was transformed into logarithms of relative risk (log RR) and the corresponding variance was calculated.[51] Where no estimates were reported, the crude estimates were calculated from tabular data, using asymptotic Mantel-Haenszel methods to evaluate the 95% CI of the log odds ratio.

The homogeneity of the effects across studies was assessed using the large sample test based on the χ^2-test. The summary relative risk was estimated using random effects models even when heterogeneity was found to be not statistically significant, in order to be conservative. Publication bias was investigated by funnel plot regression.[52]

TABLE I – METHOD USED FOR THE LITERATURE SEARCH

The literature to March 2006 was searched using the following databases: Pubmed, ISI Web of Science (Science Citation Index Expanded), Embase, Pascal, Cochrane library, Lilacs and Medcarib. The following keywords and their corresponding French translation were used for search in the PASCAL database: skin cancer, squamous cell carcinoma, SCC, basal cell carcinoma, BCC and melanoma for diseases. To define exposure, the following keywords were used: sunbed, sunlamp, artificial UV, artificial light, solaria, solarium, indoor tanning, tanning bed, tanning parlour, tanning salon and tanning booth.

Search for keywords in the title and in the abstract was done systematically. Manual search was done of references cited in the selected articles, and in selected reviews or books on melanoma and skin cancer. All participants of the working group were asked to report any additional published or submitted study. No language restriction was applied.

Primary inclusion criteria were developed for the selection of relevant articles, which were case–control, cohort or cross-sectional studies published as an original article. Ecological studies, case reports, reviews and editorials were not considered eligible.

The selected articles were reviewed, and data were abstracted by means of a standardized data-collection protocol. When another article on the same study was published simultaneously, additional relevant or missing information was retrieved from the companion paper.

Studies on melanoma

We identified 23 studies on use of indoor tanning equipment and melanoma (Table II).[34,49,50,53–73] All studies used the case–control design, except for 1 cohort study.[50] A case–control study was considered population-based when cases were derived from a population-based cancer registry and controls were selected from the general population. Of these 23 studies, 4 studies were excluded from the metaanalysis because they did not include estimates of the relative risk for cutaneous melanoma associated with exposure to tanning appliances.[53,55,57,62]

Studies used for the metaanalysis included a total of 7,355 cases. The first study was published in 1981 and the last in 2005. Fifteen studies were carried out in European countries, 4 of which in Scandinavian countries, and 2 were in the United States, 1 in Canada and 1 in Australia.

Studies on basal cell and squamous cell carcinomas

Nine case–control studies have examined the association between indoor tanning and either BCC or SCC of the skin.[74–82] All studies reported a risk estimate except one,[74] which was therefore excluded. A further 3 studies that did not distinguish between

TABLE II – CHARACTERISTICS OF THE STUDIES CONSIDERED FOR THE METAANALYSIS ON MELANOMA

Reference	Country	Number		Relative risk[2]
		Cases	Controls	
Cohort study				
Veierød *et al.* (2003)[50]	Norway, Sweden	187	106,379[1]	1.55 (1.04–2.32)
Population-based case–control studies				
Adam *et al.* (1981)[54]	UK	169	207	2.93 (1.16–7.40)
Gallagher *et al.* (1986)[55]	Canada	595	595	[3]
Holman *et al.* (1986)[56]	Australia	511	511	1.1 (0.6–1.8)
Osterlind *et al.* (1988)[59]	Denmark	474	926	0.73 (0.53–1.01)
Zanetti *et al.* (1988)[60]	Italy	208	416	0.9 (0.4–2.0)
Beitner *et al.* (1990)[62]	Sweden	523	505	[3]
Walter *et al.* (1990)[63]	Canada	583	608	[4]
Westerdahl *et al.* (1994)[70]	Sweden	400	640	1.3 (0.9–1.8)
Holly *et al.* (1995)[68]	USA	452	930	0.94 (0.74–1.2)
Chen *et al.* (1998)[69]	USA	624	512	1.13 (0.82–1.54)
Walter *et al.* (1999)[64]	Canada	583	608	1.54 (1.16–2.05)
Westerdahl *et al.* (2000)[73]	Sweden	571	913	1.2 (0.9–1.6)
Other case-control studies				
Klepp and Magnus (1979)[53]	Norway	78	131	[3]
Holly *et al.* (1987)[57]	USA	121	139	[3]
Swerdlow *et al.* (1988)[58]	UK	180	120	2.94 (1.41–6.17)
MacKie *et al.* (1989)[61]	UK	280	180	1.3 (0.2–7.9) for men; 1.2 (0.5–3.0) for women
Dunn-Lane *et al.* (1993)[65]	UK	100	100	1.16 (0.54–2.47)
Garbe *et al.* (1993)[66]	Germany	280	280	1.5 (0.9–2.4)
Autier *et al.* (1994)[67]	Belgium, France, and Germany	420	447	0.97 (0.71–1.32)
Naldi *et al.* (2000)[71]	Italy	542	538	0.78 (0.45–1.37)
Kaskel *et al.* (2001)[49]	Germany	271	271	1.00 (0.6–1.8)
Bataille *et al.* (2004)[72]	UK	413	416	1.19 (0.84–1.68)
Bataille *et al.* (2005)[34]	Belgium, France, the Netherlands, Sweden, UK	597	622	0.90 (0.71–1.14)

ALM, acral lentiginous melanoma; HC, histologically confirmed; LMM, lentigo maligna melanoma; M, melanoma; MM, malignant melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.

[1]Cohort size.–[2]Values in parentheses are 95% CI .–[3]Because no estimate of risk was reported in these studies, we did not include them in the metaanalysis.–[4]The study by Walter *et al.* (1990)[63] was reanalyzed in the 1999 publication. We used the relative risk adjusted for potential confounders presented in the 1999 publication.

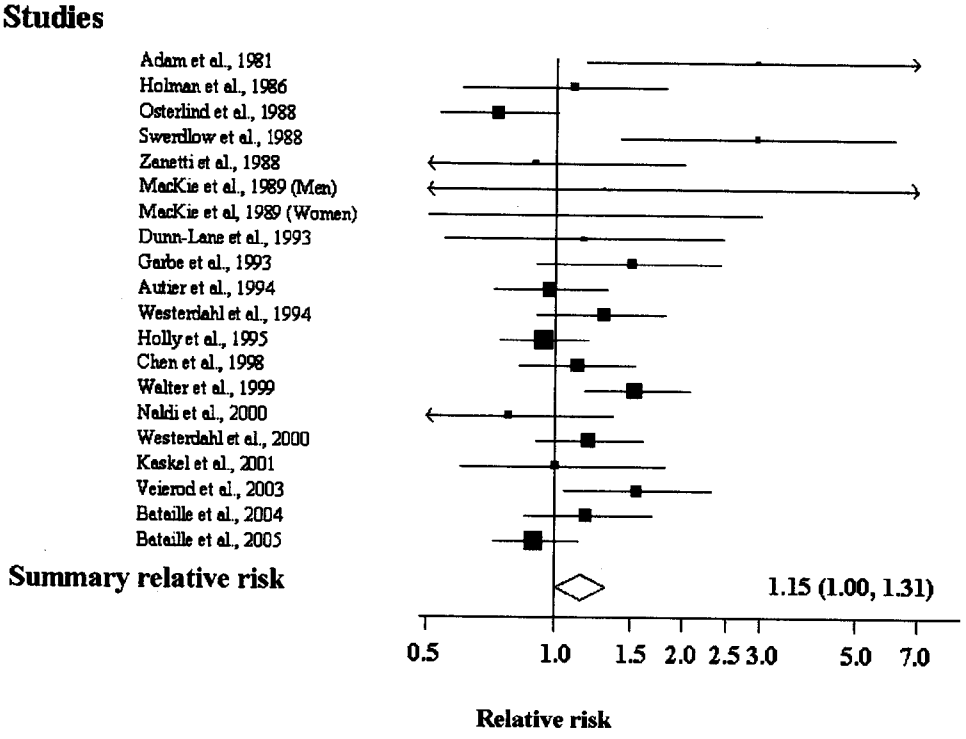

FIGURE 1 – Relative risk for cutaneous melanoma associated with ever use of indoor tanning equipment: estimates of 19 studies and summary estimate (relative risks were presented separately for men and women in the study by MacKie *et al.*[61]).

TABLE III – METAANALYSIS OF EPIDEMIOLOGICAL STUDIES ON INDOOR TANNING AND RISK FOR MELANOMA, SQUAMOUS CELL CARCINOMA AND BASAL CELL CARCINOMA

Exposure	Number of studies	Summary relative risk[1]	Heterogeneity[2] (p value)
Melanoma			
Ever use of indoor tanning equipment	19	1.15 (1.00–1.31)	0.013
First exposure in youth	7	1.75 (1.35–2.26)	0.55
Exposure distant in time	5	1.49 (0.93–2.38)	0.018
Exposure recent in time	5	1.10 (0.76–1.60)	0.81
Squamous cell carcinoma			
Ever use of indoor tanning equipment	3	2.25 (1.08–4.70)	0.10
Basal cell carcinoma			
Ever use of indoor tanning equipment	4	1.03 (0.56–1.90)	0.06

[1]Values in parentheses are 95% CI.–[2]χ^2-test: the degrees of freedom are given by the number of risk estimates included minus 1.

these 2 major types of skin cancer[75–77] were also excluded from review, leaving 5 studies for consideration.

Relative risk for melanoma

Thirteen of 19 studies presented positive estimates for "ever" *versus* "never" exposed to indoor tanning equipment, but only 4 were statistically significant[50,54,58,64] (Fig. 1). Seven of these studies reported only crude relative risks, and 1 adjusted for age and sex only. Results of the metaanalysis are shown in Table III. The summary estimate indicated a significant positive association between "ever" *versus* "never" indoor tanning and melanoma (RR, 1.15; CI, 1.00–1.31) and the χ^2-test for heterogeneity was statistically significant.

To decrease the influence of possible biases, estimates were calculated including only the cohort and the 9 population-based case–control studies. The summary relative risk was very similar apart from having wider CIs (RR, 1.17; CI, 0.96–1.42). In an analysis restricted to the 8 studies that adjusted for confounders related to sun exposure and sun sensitivity,[50,60,61,64,69–71,73] the summary relative risk remained similar to that obtained from all 19 studies, but the CI widened (RR, 1.19; CI, 0.33–4.30).

Seven studies presented estimates relevant for the evaluation of "first exposure in youth" *versus* "never" (Fig. 2). All relative risks were adjusted for confounders related to sun exposure or sun sensitivity, except in the study by Walter *et al.*[64] A significant 75% increase in risk was detected (Table III) and the χ^2-test for heterogeneity was nonsignificant.

Five studies investigated time since exposure and reported estimates that allowed comparisons between recent and more distant exposure.[34,58,63,67,69] Metaanalytic estimates were greater for exposures more distant in time when compared to those for more recent exposures (Table III).

There was some indication for a dose-effect relationship in 2 studies,[67,70] but not in the other two.[69,73] But metrics used for assessing duration were all different and therefore did not permit metaanalytic synthesis. Only 4 studies explored the role of natural sensitivity to sunlight on risk associated with indoor tanning, and overall, they found no consistent result.[34,64,72,73]

Type of indoor tanning equipment

No epidemiological study has been able to explore in a rigorous way amounts of UVA and UVB received by indoor tanning users. The study by Chen *et al.*[69] obtained information concerning the type of sunbed or sunlamp used (*e.g.*, desktop models, floor models, beds or walk-in booths). This information was obtained by showing to subjects pictures of various types of sunlamps and sun-

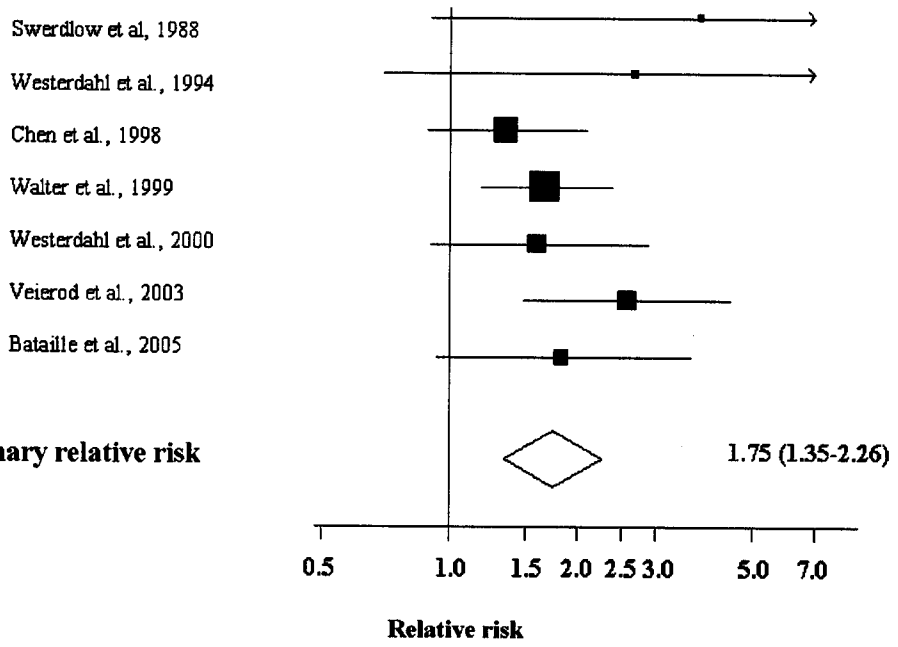

FIGURE 2 – Relative risk for cutaneous melanoma associated with first use of indoor tanning equipment at age <35 years: estimates of 7 studies and summary estimate.

beds. The study found a nonsignificant elevated risk of malignant melanoma associated with the use of desktop sunlamps and heavyweight floor-model sunbeds and a statistically significant tripled risk associated with use of more than 2 types of sunlamps, compared with no use of sunbeds. The study by Bataille *et al.*[34] reported no impact of the type of device used on melanoma risk.

The relative risks of melanoma associated with ever-use of sunbed/sunlamp reported in the studies did not vary with year of publication or first year of study period, and funnel plot regression gave no indication of publication bias (ever-use of sunbed/sunlamps, $p = 0.80$; first exposure in youth, $p = 0.10$). This observation suggests that the apparent increased risk for ever use and for age at first use were unlikely to be explained by the earlier types of indoor tanning appliance used.

Before 1980, exposure to artificial UV radiation was more likely to take place at home with devices that emitted greater amounts of UVB radiation, whereas exposure in the 1980s increasingly occurred in commercial salons using equipment that emitted mainly UVA. The Norway–Swedish prospective study provided evidence that the increased melanoma risk associated with exposure to tanning appliances was not due to the type of UV lamps used before 1983.[83]

Relative risk for squamous cell carcinoma and basal cell carcinoma

The metaanalysis was based on the 5 studies[78–82] reporting type-specific risk estimates (Table III). Metaanalytic estimates suggested a significant effect of exposure to indoor tanning appliances for SCC, but not for BCC. Funnel plot regression gave no indication of publication bias ($p = 0.26$ and 0.77 for SCC and BCC, respectively).

The study by Karagas *et al.*[81] gave the most detailed results, and the trends were consistent with the results reported for melanoma. Results were adjusted for sun sensitivity but not for sun exposure, since adjustment for sun exposure did not change the risk estimates. Depending on age at first use, the risks for BCC and SCC were found to increase by 10% (OR, 1.1; CI, 0.9–1.5) and 20% (OR, 1.2; CI, 0.9–1.6) respectively for each decade younger the person was at first use of indoor tanning equipment.

Discussion

Investigation of the association between indoor tanning and skin cancers poses challenging problems, as indoor tanning has been in widespread use only recently. Based on our knowledge about the relationship between sun exposure and risk for melanoma, it could be stated that associations after long latency periods, such as would be expected for melanoma and BCC, may not be detectable yet. Also, since the fashion of indoor tanning has been increasing steadily, the failure to distinguish between distant and recent exposures in most epidemiological studies may mask an actual increase in risk with exposure early in life.

Our systematic review of published studies mainly from Europe and North America of the association of use of indoor tanning equipment with skin cancers revealed an association of age at first use of less than 35 years with melanoma risk. These studies consistently indicated a moderate strength of association, with a summary relative risk of 1.75 (1.35–2.26). This result suggests a greater vulnerability of younger people to the carcinogenic impact of indoor tanning. Also, it is in agreement with the knowledge that age at exposure may influence the relative risk for skin cancer associated with UV exposure, and that exposure to sunlight in childhood is an important contributing factor for melanoma risk in adults.[84,85]

The association with ever-use of such equipment, or use more than 15–20 years prior to diagnosis of melanoma, was weak, and evidence regarding a dose–response relationship was scant. The evidence is limited by concerns over characterization of exposure and recall of exposure by individuals, potential confounding by sun exposure or other variables and the low power to detect associations that become evident only following a prolonged lag period after exposure. Our results are similar to a previous metaanalysis,[86] but our systematic review is more exhaustive and included more studies.

In Scandinavian countries use of indoor tanning equipment has been popular since the late 1970s and the prevalence of use in those countries is the highest in the world. In the Norwegian–Swedish prospective study the highest risk for melanoma was found in women who used indoor tanning equipment at least once per month when they were 20–29 years old. These results support the hypothesis that a certain lag period is needed before the impact

of exposure to tanning appliances on melanoma incidence becomes apparent. It also underlines the greater vulnerability of younger subjects to harmful effects of indoor tanning.

The positive association between use of indoor tanning equipment and melanoma risk reported here is consistent with the knowledge that melanoma is caused primarily by exposure to solar radiation. The limited evidence for a positive association between indoor tanning and SCC is consistent with its known dependence on dose of UV radiation to the skin. Thus the biological plausibility of a causal association between indoor tanning and risk for melanoma and SCC is strong.

On balance, the evidence pertaining to the strength, consistency, dose–response and temporal sequence of the association of the use of indoor tanning equipment with melanoma risk, and of the coherence and biologic plausibility of the association, leads us to conclude that there is convincing evidence to support a causal relationship, particularly with exposure before the age of 35 years. This evidence is strongly suggestive and further studies could clarify our understanding of this association and allow more definitive conclusions.

We are cognizant of the importance of this issue for the health of light-skinned populations. The strength of the existing evidence suggests that policy makers should strongly consider enacting measures such as restricting minors and discouraging young adults from using indoor tanning equipment, in order to protect the general population from additional risk for melanoma and squamous cell skin cancer.

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BMJ 2012;345:e4757 doi: 10.1136/bmj.e4757 (Published 24 July 2012)

RESEARCH

Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis


OPEN ACCESS

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Abstract

Objective To estimate the burden of melanoma resulting from sunbed use in western Europe.

Design Systematic review and meta-analysis.

Data sources PubMed, ISI Web of Science (Science Citation Index Expanded), Embase, Pascal, Cochrane Library, LILACS, and MedCarib, along with published surveys reporting prevalence of sunbed use at national level in Europe.

Study selection Observational studies reporting a measure of risk for skin cancer (cutaneous melanoma, squamous cell carcinoma, basal cell carcinoma) associated with ever use of sunbeds.

Results Based on 27 studies ever use of sunbeds was associated with a summary relative risk of 1.20 (95% confidence interval 1.08 to 1.34). Publication bias was not evident. Restricting the analysis to cohorts and population based studies, the summary relative risk was 1.25 (1.09 to 1.43). Calculations for dose-response showed a 1.8% (95% confidence interval 0% to 3.8%) increase in risk of melanoma for each additional session of sunbed use per year. Based on 13 informative studies, first use of sunbeds before age 35 years was associated with a summary relative risk of 1.87 (1.41 to 2.48), with no indication of heterogeneity between studies. By using prevalence data from surveys and data from GLOBOCAN 2008, in 2008 in the 15 original member countries of the European Community plus three countries that were members of the European Free Trade Association, an estimated 3438 cases of melanoma could be attributable to sunbed use, most (n=2341) occurring among women.

Conclusions Sunbed use is associated with a significant increase in risk of melanoma. This risk increases with number of sunbed sessions and with initial usage at a young age (<35 years). The cancerous damage associated with sunbed use is substantial and could be avoided by strict regulations.

Introduction

Exposure to the sun is the most important environmental cause of skin cancer, with the wavelength for ultraviolet radiation associated with development of the disease.[1] The wavelengths for ultraviolet radiation range between 100 nm and 400 nm and are broadly categorised into ultraviolet A light (315-400 nm), ultraviolet B (280-315 nm), and ultraviolet C (100-280 nm). All ultraviolet C and most ultraviolet B wavelengths are blocked by the stratospheric ozone layer. A fraction of ultraviolet B and all ultraviolet A reaches the Earth's surface.

In light skinned populations, the ultraviolet radiation delivered by sunbeds has become the main non-solar source of exposure to ultraviolet light. Indoor tanning has been widely practised in northern Europe and the United States since the 1980s,[2] and since 2000 this trend has gained popularity in sunnier countries, such as Australia.[3 4] Modern indoor tanning equipment mainly emits in the ultraviolet A range, but a fraction (<5%) of this spectrum is in the ultraviolet B range. This ultraviolet B fraction induces a deep, long lasting tan. Powerful ultraviolet tanning units may be 10-15 times stronger than the midday sunlight on the Mediterranean Sea, and repeated exposure to large amounts of ultraviolet A delivered to the skin in relatively short periods (typically 10-20 minutes) constitutes a new experience for humans.

Indoor tanning has a plethora of negative health effects, many of which are involved in cancerous processes.[5] The impact of this trend on incidence of skin cancer is of concern, mainly because of cutaneous malignant melanoma, a cancer of poor prognosis when diagnosed at an advanced stage.

Until recently ultraviolet B was usually considered the only carcinogenic fraction of the solar spectrum reaching the Earth's surface. In 2009, the International Agency for Research on Cancer classified the whole ultraviolet spectrum and indoor tanning devices as carcinogenic to humans (group 1).[6] The rationale for classifying ultraviolet A and sunbeds as group 1 carcinogens was based on congruent lines of evidence from basic and epidemiological research. Briefly, extensive laboratory data and animal experiments (on DNA mutations and repair, immune function, cell integrity, cell cycle regulation, and other critical biological functions) documented a role for ultraviolet A in skin carcinogenesis[7-9] and that the body's repair and

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removal of damaged DNA was less effective when the damage was caused by ultraviolet A rather than by ultraviolet B.[10] Experiments in human volunteers showed that exposure to ultraviolet A and ultraviolet B can weaken the immune system through mechanisms that interact and overlap, increasing vulnerability to cancer as well as to other diseases.[11] Also, tanning lamps induce the types of DNA damage to the skin associated with photocarcinogenesis.[11] Lastly, the meta-analysis undertaken in 2005 found a significant 75% increase in risk of melanoma (from 40% to 228%) when indoor tanning started during adolescence or young adulthood.[11 12] Some evidence was also found that indoor tanning increased the risk of squamous cell carcinoma, especially when sunbed use started before the age of 20.

The meta-analysis by the International Agency for Research on Cancer in 2006 could not examine dose-responses, and additional epidemiological studies published since then have provided an opportunity for some aspects of the relation between sunbed use and melanoma to be explored in greater depth. Using meta-analysis we quantified the risk of melanoma associated with indoor tanning using artificial ultraviolet light, including dose-response and the estimated burden of melanoma and death associated with sunbed use in western Europe.

Methods

To update the meta-analysis of 2006, we used the same methodological approach as previously described.[11] Briefly, MB searched the literature published up to May 2012 using the databases PubMed, ISI Web of Science (Science Citation Index Expanded), Embase, Pascal, Cochrane Library, LILACS, and MedCarib. We used the following keywords for diseases: "skin cancer", "squamous cell carcinoma", "SCC", "basal cell carcinoma", "BCC", and "melanoma". To define exposure, we used the following keywords: "sunbed", "sunlamp", "artificial UV", "artificial light", "solaria", "solarium", "indoor tanning", "tanning bed", "tanning parlour", "tanning salon", and "tanning booth". No language restriction was applied. We reviewed the titles and abstracts to identify potentially eligible studies and carried out a manual search of studies identified from references cited in reviews on skin cancer.

From the initial search we selected case-control, cohort, and cross sectional studies published as original articles. Non-eligible trials included ecological studies, case reports, reviews, and editorials.

PA and SG reviewed the selected articles and SG and MB abstracted the data using a standardised data collection protocol. The minimal common information on use of indoor tanning appliances for all studies was "ever used." For those studies that did not strictly assess ever users of indoor tanning appliances compared with never users,[13 14] we used the information closest to this category.

We also extracted the highest category of sunbed use reported in each study—that is, the greater duration (defined as "high use") along with estimates of risk for the association with first use of sunbeds at a young age—before age 35 years.

Statistical analysis

We transformed every measure of association, adjusted for the maximum number of confounding variables, and 95% confidence intervals, into logarithms of relative risk and calculated the corresponding variance.[15] When no estimates were reported, we used tabular data to calculate the crude estimates and 95% confidence intervals.

The meta-analysis was calculated from a random effect model as described previously[16]—that is, a mixed effects model with summary relative risk obtained from maximum likelihood estimation. We calculated confidence intervals assuming an underlying t distribution. Heterogeneity was assessed by Higgins and Thompson's I^2 statistic.[17] The I^2 statistic ranges from zero to 100%, zero indicating that the relative risks of the different studies included in the meta-analysis are homogeneous—that is, that the relative risks are consistent with each other.

We used a two step procedure to obtain summary risk estimates for dose-response. Firstly, we fitted a linear model within each study to estimate the relative risk per session of sunbed use. When sufficient information was published (the number of participants in usage category), we fitted the model according to a previously proposed method.[18] This method provides the natural logarithm of the relative risk and an estimator of its standard error, taking into account that the estimates for separate categories depend on the same reference group. When the numbers of participants in each serum level category were not available from the publications, we calculated coefficients ignoring the correlation between the estimates of risk at the separate exposure levels. Secondly, we estimated the summary relative risk by pooling the study specific estimates with the mixed effects models.

All analyses were done with SAS Windows version 9.2. We used PROC MIXED in SAS to calculate the random effects models.

Heterogeneity and sensitivity analyses

We carried out several sensitivity analyses to evaluate the stability of the pooled estimates. Firstly we examined the pooled relative risks for case-control and prospective (cohort and nested case-control) studies separately. Then we examined changes to the results after the exclusion of specific studies.

To investigate heterogeneity between the studies we carried out metaregressions and subgroup analyses. Heterogeneity was investigated by looking at factors that could influence the quality of the studies and that could be responsible for heterogeneity, such as the study design, adjustment for confounding factors, features of the population, and publication year. As an additional analysis for heterogeneity, we compared risk estimates according to the average latitude of countries or areas where studies were done.

To investigate whether publication bias may have affected the validity of the estimates, we constructed funnel plots of the regression of log relative risk on the sample size, weighted by the inverse of the pooled variance. We evaluated publication bias using the Macaskill test.[19]

Sunbed use and burden of melanoma

To translate the estimation of risk in the current study to the burden in the general population, we provided a broad estimation of the burden of sunbed use in Europe. We gathered data on the prevalence of sunbed use from recent surveys carried out in Europe. As no survey was available for central European countries, we limited our estimation to the original 15 countries of the European Community (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Spain, Sweden, Portugal, the Netherlands, and the United Kingdom) plus the three countries that are part of the European Free Trade Association (Iceland, Norway, and Switzerland). For these 18 countries, we extracted data on the incidence of melanoma from GLOBOCAN 2008.[20]

We identified seven surveys carried out in the 18 countries from which we extracted prevalence of ever having used a sunbed during lifetime.[21-27] We also extracted the prevalence of sunbed use in the control group included in the Swedish cohort.[14] Data were available for Denmark, France, Germany, Iceland, Spain, Sweden, Switzerland, and the United Kingdom. These countries represent 70% of all melanoma cases occurring in the 18 countries studied. Prevalence for the other 10 countries was determined from estimates for neighbouring countries.

We estimated the attributable fraction with Levin's formula[28] by using prevalence of ever use of sunbeds from surveys and the summary relative risk for ever use of sunbeds.

Results

Figure 1⇓ describes the literature search process. Since the meta-analysis of 2006, eight additional studies were identified, one of which was the update of the Norwegian-Swedish cohort.[29] Thus in May 2012, 32 studies had investigated the relation between sunbed use and melanoma (table 1⇓). All studies were based on the case-control design except three, which were cohort studies.[14 50 59] The Nurse's Health Study was based on a cohort design but the trial was a case-control study with retrospective assessment of sun exposure and sunbed use in samples of skin cancer cases and controls matched on year of birth.[42] One study was a survey among patients attending a dermatology clinic.[53] One third of patients participated in the survey. Sunbed use of patients with a diagnosis of cutaneous melanoma was compared with that of other patients. Although this study was not in the broadest sense a case-control design, it was included in the meta-analysis.

Four of the 32 studies[13 14 30-59] were excluded from the meta-analysis because they did not include estimates of the relative risk for cutaneous melanoma associated with sunbed use.[34 44 46 40] One study[55] was redundant as it was reanalysed and published in 1999.[54]

Studies used for meta-analysis totalled 11 428 cases of melanoma. The first study[30] was published in 1981 and the last[59] in 2012. Eighteen studies were carried out in European countries, seven in the United States and Canada, and two in Australia.

Summary relative risks

Twenty seven studies presented positive estimates for ever use compared with never use of sunbeds (fig 2⇓). Eight of these studies reported only crude relative risks and one adjusted for age and sex only. The summary relative risk was 1.20 (95% confidence interval 1.08 to 1.34), with heterogeneity (I^2=56%). Evidence of publication bias was lacking (P=0.99, Macaskill test). An analysis restricted to the 18 cohort and population based case-control studies produced a slightly higher summary relative risk (1.25, 1.09 to 1.43). An analysis restricted to the 18 studies that adjusted for confounders related to sun exposure and sun sensitivity yielded a similar summary relative risk (1.29, 1.13 to 1.48).

When the cohort studies were excluded from the analysis the summary relative risk decreased slightly but remained statistically significant (1.20, 1.06 to 1.37).

Thirteen studies presented estimates relevant for the evaluation of first use of sunbeds in youth (before age 35) compared with never use (fig 3⇓). All relative risks were adjusted for confounders related to sun exposure or sun sensitivity, except in one study.[54] The risk was almost doubled (relative risk 1.87), with no indication of heterogeneity (I^2=0).

Four studies reported data on risk associated with the number of sunbed sessions per year. A summary relative risk derived from relative risks reported for each session was 1.018 (95% confidence interval 0.998 to 1.038), which indicated a 1.8% increase in risk of melanoma for each annual session. A significant 42% increased risk was found for high use of sunbeds (summary relative risk 1.42, 95% confidence interval 1.15 to 1.74; fig 4⇓). Nine studies reported risks associated with time since first use, with first use distant in time (that is, more than five years before diagnosis) associated with a higher summary relative risk (1.49, 1.18 to 1.88; I^2=34%) than first use more recently (1.18, 0.95 to 1.48; I^2=51%, table 2⇓).

Risks for sunbed related melanoma were compared in populations living at different latitudes (fig 5⇓). Relative risks associated with ever versus never use of sunbeds did not differ much with variations in latitude and there was no indication that risks would be higher in more sun sensitive populations such as those in the Nordic countries.

Sensitivity analysis

The summary relative risk remained significant when all possible studies, including publications with missing estimates, were included and a relative risk of 1 (no effect) was imputed for the missing relative risks (1.20, 1.10 to 1.34).

Squamous and basal cell carcinomas

Two studies[42 59] published since 2005 looked at the risk of non-melanoma skin cancer associated with sunbed use. Adding data from this study to that of the 2006 meta-analysis[11] yielded summary relative risks for ever versus never sunbed use of 2.23 (1.39 to 3.57) for squamous cell carcinoma (1242 cases in five studies)[42 59-62] and 1.09 (1.01 to 1.18) for basal cell carcinoma (6995 cases in six studies).[42 59 61-64]

Impact on burden of melanoma in western Europe

Of 63 942 new cases of cutaneous melanoma diagnosed each year in the 15 countries that were members of the European Community and the three countries that were part of the European Free Trade Association, an estimated 3438 (5.4%) were related to sunbed use (table 3⇓). Women represented most of this burden, with 2341 cases (6.9% of all melanoma cases in women) related to sunbed use; 1096 cases annually occurred in men (3.7% of all cases in men). Taking a melanoma incidence to mortality ratio of 3.7 for European men and 4.7 for European women,[20] in the 15 European Community countries, about 498 women and 296 men would die each year from a melanoma as a result of being exposed to indoor tanning using artificial ultraviolet light.

Discussion

Overall, the summary of results of 27 observational studies published within the past 30 years shows that the risk of cutaneous melanoma is increased by 20% for those who were ever users of indoor tanning devices with artificial ultraviolet light. The risk of melanoma was doubled when use started before the age of 35 years. This latest estimate originates from studies in various populations and latitudes, which obtained consistent results with zero heterogeneity. Summary risk estimates calculated from population based case-control studies were close to those of cohort studies.

Comparison with 2006 evaluation

The 2006 evaluation[11] did not find evidence for a dose-response relation between the level of sunbed use and risk of melanoma; however, a formal metaregression analysis could not be carried out because not enough data were published at that time. Since then, large studies have provided data consistent with a dose-response relation—for example, a study in Minnesota[47] found dose-responses for years during which sunbeds were used, cumulative time (hours) of sunbed use, and cumulative number of tanning sessions.

Table 2 summarises the results of the meta-analyses of 2006[11] and of this meta-analysis. From 2005 to 2011, most summary relative risks have increased. These changes support the hypothesis that earlier studies tended to underestimate risks associated with indoor tanning because this behavioural trend is relatively new and thus recent uses may not (yet) have influenced the incidence of melanoma.[11 65] From this logic it is possible that future epidemiological studies on sunbed use and skin cancer could show relative risks higher than those found to date.

Risk of melanoma associated with sunbed use in different populations

We did not observe a significant difference in risk when taking latitude of residence into account. Most studies included in this meta-analysis were adjusted for phototype or a proxy for sun sensitivity. In this respect, the summary relative risks presented in this article are valid for all light skinned populations such as those in Europe, North America, and Australasia. The number of melanoma cases arising from sunbed use may, however, be higher than we estimated because it seems that sunbed users are more likely to have fair skin, have red or blond hair, have more freckles, and be phototype I/II (burn easily and tan minimally if at all when first exposed to the sun) than III/IV (burn moderately and tan easily or always when first exposed to the sun) than non-users.[66]

Sunbed users also have the tendency to adopt unhealthy lifestyles compared with non-users[2] and we could hypothesise that use of sunbeds may be a marker of populations more exposed to sun. However, several studies, such as the cohort study by Veierød et al[14] (see table 1), did adjust for a variable of sun exposure. The summary relative risk is then unlikely to reflect a more intense exposure to sun among sunbed users. Compelling evidence that use of sunbeds can be a cause of melanoma and not just a proxy for sun exposure arises from the investigation of a melanoma epidemic in Iceland, a country located between 64° and 66° N and where sunny days are uncommon.[67] After 1990, the incidence of melanoma increased sharply, mainly in young women, with preferential occurrence on the trunk. The incidence tended to decline after 2000, when public health authorities imposed greater control on sunbed installation and utilisation. Although that study was an ecological one, the exposure of Icelandic youngsters that took place after 1985 seemed to be the most likely reason for that epidemic.[68]

The results of this meta-analysis are in full agreement with the considerable amount of data pointing to childhood and adolescence as the key periods for initiation and development of melanoma in adulthood.[69] This evidence on the risks of skin cancer associated with exposure to ultraviolet light at young ages underlines the health threats documented by many recent surveys, which show substantial use by children and adolescents of tanning devices using artificial ultraviolet light in the United States and European countries.[70-73] with evidence for unabated increasing use in the United States.[74] For instance, in Denmark, a survey completed in 2008 found that 2% of children aged 8 to 11 years and 13% aged 12 to 14 years had used a sunbed within the past 12 months.[72]

Burden of melanoma associated with sunbed use in Europe

In Europe, 71% of melanoma cases in 2008 occurred in the 15 European Union countries and the three European Free Trade Association countries. We estimated that in these 18 countries each year, around 3438 new cases of melanoma and 794 related deaths would be related to sunbed use. This estimation is limited to western European countries because of a lack of information on sunbed use in central European countries. The number of deaths from melanoma associated with sunbed use was determined for the United Kingdom in 2003,[75] with an estimated 100 deaths (range 50-200) annually. Our calculation of attributable fractions would put the number of deaths for the United Kingdom at 99, a figure consistent with the earlier estimate. The estimation of deaths from melanoma should be treated with caution since some epidemiological data suggest that, on average, sunbed related melanoma could be of low malignant potential.[75 76] None the less, the burden of cancer attributable to sunbed use could further increase in the next 20 years because the recent, high usage levels observed in many countries have not yet achieved their full carcinogenic effect and because usage levels of teenagers and young adults remain high in many countries. This prediction is supported by the observation over 10-15 years of increases in the incidence of melanoma on the trunks of women from countries with widespread access to indoor tanning.[67 77-80] The incidence rates of trunk melanoma in women aged 20-49 years therefore could be a relevant indicator for monitoring activities to decrease the use of sunbeds.

Indoor tanning industry and regulation

Melanoma and other skin cancers that are specifically associated with sunbed use are preventable diseases by avoiding exposure to these devices. Generally the sunbed industry has not self regulates effectively and has tended to disseminate non-evidence based information, which can deceive consumers.[81-83] Tanning salon operators simply following regulations is an illusory prevention method, as such regulations are unable to turn a carcinogenic agent into a healthy one. Instead, the sunbed industry has used the opportunity to claim that properly regulated indoor tanning is safe, and that it might even have health benefits.[81]

Discouraging sunbed use or requiring parental authorisation is not effective, partly because many parents of teenagers willing to use sunbeds are also sunbed users themselves.[2 73]

Prevention of the harmful effects associated with sunbed use must be based on tougher actions. Recommendations from the World Health Organization, the International Commission on Non-Ionizing Radiation Protection (ICNIRP), and the European Society of Skin Cancer Prevention (EUROSKIN) maintain that the highest regulatory priorities should be the restriction of sunbed use by people under 18 years of age and the banning of unsupervised indoor tanning facilities. Such restrictions have now been implemented in Australia and in several European countries (Austria, Belgium, France, Germany, Portugal, Scotland, and Spain). In the United States, until the recent ban by the state of California issued on 10 October 2011, no state had banned access to indoor tanning for adolescents aged less than 18 years.

If sunbed use by teenagers and young adults does not substantially decrease in the short term, then more radical actions should be envisioned, such as the nationwide prohibition of the public use of tanning devices, which was implemented by the Brazilian National Health Surveillance Agency[84] in November 2009.[85]

Contributors: MB, SG, and PA carried out the literature search and extracted data. MB and SG did the statistical analysis and drafted the first manuscript. All authors interpreted the data, contributed to discussion, and reviewed or edited the manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis and are guarantors for the paper.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: The statistical analysis programs in SAS are available on request from the corresponding author (mathieu.boniol@i-pri.org).

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What is already known on this topic

Earlier studies suggested an increased risk of melanoma, in particular when sunbed use started before age 35

No consistent dose-response relation was found

What this study adds

This study confirms a doubling of the risk of melanoma when first sunbed use is at a young age (<35 years)

A dose-response relation exists between amount of sunbed use and risk of melanoma

In Europe each year, 3438 new cases of melanoma would be due to sunbed use

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Accepted: 2 July 2012

Cite this as: *BMJ* 2012;345:e4757

Tables

Table 1| **Characteristics of studies on sunbed use and melanoma considered for meta-analysis**

Studies	Country	No of cases	No of controls	Adjustments
Cohort or population based case-control studies:				
Adam et al 1981[30]	UK	169	207	Crude
Gallagher et al 1986[40]*	Canada	595	595	—
Holman et al 1986[45]	Australia	511	511	Crude
Osterlind et al 1988[51]	Denmark	474	926	Not clear
Zanetti et al 1988[58]	Italy	208	416	Age, hair colour, skin reaction, sunburn in childhood, education level
Beitner et al 1990[34]*	Sweden	523	505	—
Walter et al 1990[55]*†	Canada	583	608	—
Westerdahl et al 1994[57]	Sweden	400	640	Hair colour, nevi, skin type, sunburns
Holly et al 1995[43]	USA	452	930	—
Chen et al 1998[35]	USA	624	512	Age, sex, phenotype, recreational sun exposure
Walter et al 1999[54]	Canada	583	608	Age, sex, and skin reaction
Westerdahl et al 2000[56]	Sweden	571	913	Sunburns, hair colour, sunbathing
Han et al 2006[42]	USA	200	804	Age, sex, family history, hair colour, sun exposure
Clough-Gorr et al 2008[36]	USA	423	678	
Cust et al 2011[37]	Australia	604	479	—
Lazovich et al 2010[47]	USA	1167	1101	Age, sex, family history, hair colour, sun exposure
Veierød et al 2010[14]	Norway, Sweden	412	106 366‡	Age, residence, hair colour, sunburns, annual "bathing" holiday
Elliott et al 2011[39]	UK	959	513	Age, sex, educational level, family history of melanoma, sun sensitivity, and sun exposure
Nielsen et al 2011[50]	Sweden	210	29 520‡	Crude
Zhang et al 2012[59]	USA	349	73 494‡	Age, family history, hair colour, number of moles, sunburn tendency and history, outdoor sun exposure, ultraviolet index, state of residence at birth, age 15, and age 30
Other case-control studies:				
Klepp and Magnus 1979[46]*	Norway	78	131	—
Holly et al 1987[44]*	USA	121	139	—
Swerdlow et al 1988[52]	UK	180	120	Crude
MacKie et al 1989[48]	UK	280	180	Nevi, skin type, sunburn, freckles, tropical residence
Dunn-Lane et al 1993[38]	UK	100	100	Crude
Garbe et al 1993[41]	Germany	280	280	Nevi, hair type, and phototype§
Autier et al 1994[31]	Multicentre	420	447	Crude
Naldi et al 2000[49]	Italy	542	538	Age, sex, skin, hair, eye, nevi, freckles, sunburns, number of holidays in sunny climates
Kaskel et al 2001[13]	Germany	271	271	Crude
Bataille et al 2004[33]	UK	413	416	Sex and age
Bataille et al 2005[32]	Belgium, France, Netherlands, Sweden, UK	597	622	Sex, age, and skin phototype§
Ting et al 2007[53]	USA	29	307	Not clear

*Not included in main meta-analysis as no estimate of risk was reported.

†1990 study was reanalysed in 1999. Present meta-analysis uses relative risk adjusted for potential confounders presented in 1999 publication.

‡Cohort size.

Table 1 (continued)

Studies	Country	No of cases	No of controls	Adjustments

§Sensitivity to sunlight.

Table 2| **Summary relative risks found by meta-analyses on sunbed use and cutaneous melanoma**

Sunbed use	No of studies in 2005 meta-analysis*	Summary relative risk (95% CI)	No of studies in present meta-analysis	Summary relative risk (95% CI)	I^2 (%)
Ever use	19	1.15 (1.00 to 1.31)	27	1.20 (1.08 to 1.34)	56
Ever use†	10	1.17 (0.96 to 1.42)	18	1.25 (1.09 to 1.43)	60
First use in youth (<35 years)	7	1.75 (1.35 to 2.26)	13	1.87 (1.41 to 2.48)	0
High use	NR	NR	14	1.42 (1.15 to 1.74)	—
First use recently	5	1.10 (0.76 to 1.60)	9	1.18 (0.95 to 1.48)	51
First use distant in time‡	5	1.49 (0.93 to 2.38)	9	1.49 (1.18 to 1.88)	34

NR=not reported.

*International Agency for Research on Cancer, 2006.

†Cohort or population based case-control studies only.

‡More than five years before diagnosis.

Table 3| **Estimation of number of melanoma cases attributed to sunbed use in Europe**

Population	Attributable fraction (%)*		Incidence case caused by ever use of sunbeds		
	Men	Women	Men	Women	Total
Austria†	6.5	10.6	34	52	86
Belgium†	6.5	10.6	41	102	143
Denmark	8.1	13.0	52	106	157
Finland‡	5.8	9.4	29	43	72
France	1.4	3.8	47	157	203
Germany	6.5	10.6	500	904	1404
Greece§	0.4	1.3	1	3	3
Iceland	3.9	6.1	1	1	2
Ireland	1.6	5.8	5	25	30
Italy§	0.4	1.3	15	52	67
Luxembourg†	6.5	10.6	2	4	6
Norway‡	5.8	9.4	38	57	95
Portugal§	0.4	1.3	1	7	8
Spain	0.4	1.3	6	26	32
Sweden	5.8	9.4	71	113	184
Switzerland	5.1	8.7	54	101	155
Netherlands†	6.5	10.6	114	231	345
United Kingdom	1.6	5.8	87	357	444
Total			1096	2341	3438

*Calculated from relative risk determined in present meta-analysis and various surveys on prevalence of sunbed use in population.

†Prevalence data for Germany were used for Austria, Luxembourg, Belgium, and Netherlands.

‡Prevalence data for Sweden were used for Finland and Norway. As no data were reported for men, we applied the male:female ratio from Germany survey to Sweden prevalence data.

§Prevalence data for Spain were used for Greece, Italy, and Portugal.

Figures

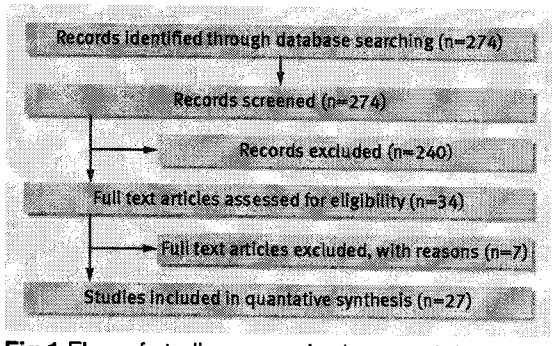

Fig 1 Flow of studies on sunbed use and risk of cutaneous melanoma

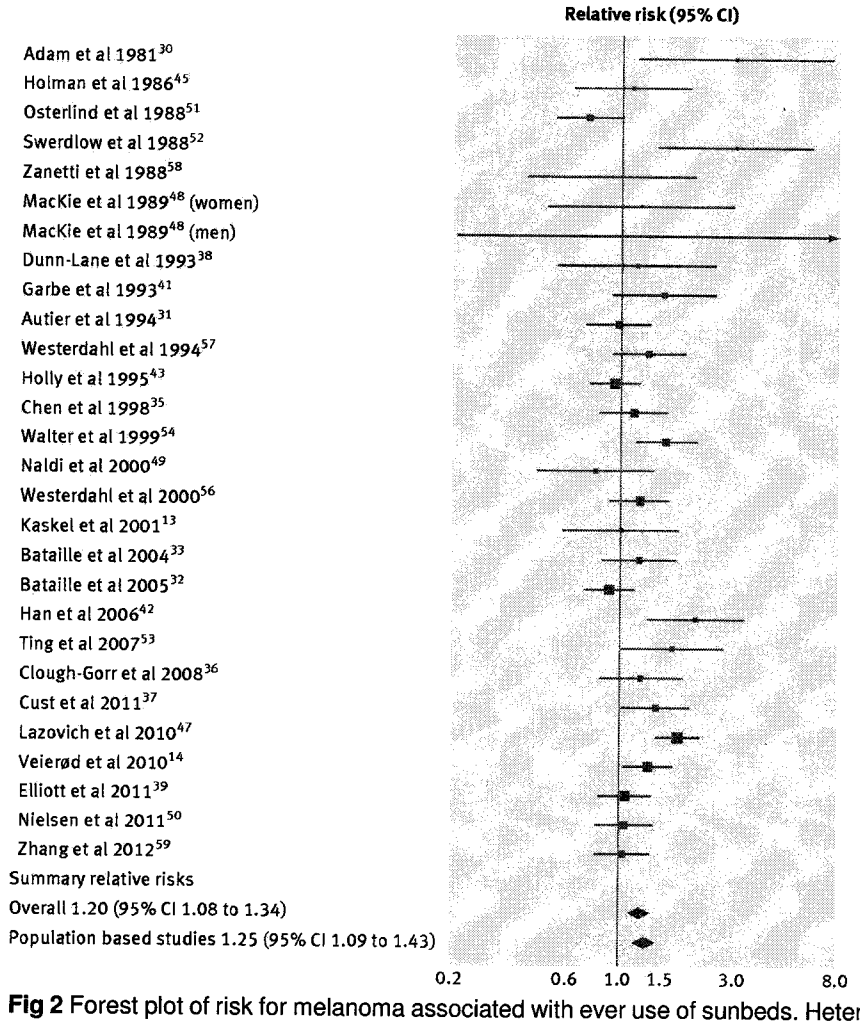

Fig 2 Forest plot of risk for melanoma associated with ever use of sunbeds. Heterogeneity I^2=57% for all studies combined

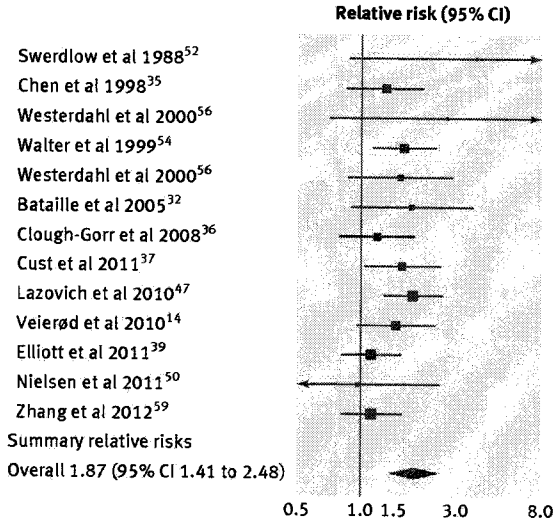

Fig 3 Forest plot of risk for melanoma associated with ever use of sunbeds when first use was before age 35 years. No heterogeneity (I^2=0)

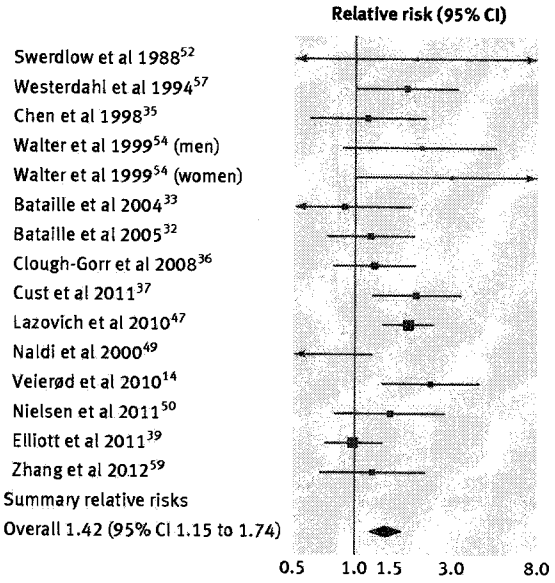

Fig 4 Forest plot of risk for melanoma associated with high use of sunbeds. Heterogeneity I^2=47%

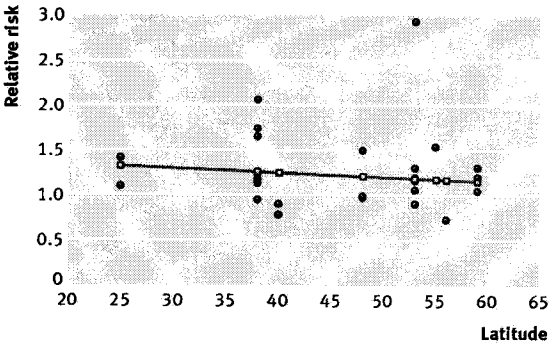

Fig 5 Risk for melanoma associated with ever use of sunbeds as a function of latitude